# PALLADIUM-CATALYZED REGIOSELECTIVE CARBONYLATIVE COUPLING OF ALKYNES WITH ANILINE DERIVATIVES

BY

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A Thesis Presented to the

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**KING FAHD UNIVERSITY OF PETROLEUM & MINERALS**

DHAHRAN, SAUDI ARABIA

In Partial Fulfillment of the
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# MASTER OF SCIENCE

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This thesis, written by **Mr. Jimoh Tijani** under the direction of his Thesis Advisor and approved by the thesis committee, has been presented to and accepted the Dean of Graduate studies, in partial fulfillment of the requirements for the degree of **MASTER OF SCIENCE IN CHEMISTRY**.

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MY PARENTS

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Praise be to Allah Almighty, The all Knowing. Blessing and peace be upon our leader Muhammad, his family, his companions, and those that follow his guidance until the last day.

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**Name of student:** **Jimoh Tijani**

**Title of study:** **Palladium-Catalyzed Regioselective Carbonylative Coupling of Alkynes with Aniline Derivatives**

**Major field:** **Chemistry**

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Carbonylation reactions rank among the most useful transformations homogeneously catalyzed by transition-metal complexes. It is an efficient method for the direct introduction of the carbonyl moiety into organic molecules. Direct carbonylative coupling of alkynes with amines yield unsaturated amides. Highly toxic $Ni(CO)_4$, nickel halides, $Ni(CN)_4$ and $Co_2(CO)_8$ were used, but their activity were very low and therefore, they required severe reaction conditions. Aminocarbonylation of terminal alkynes proceeded regioselectively in the presence of palladium complexes and iodide as promoter; contamination by the volatile iodine compounds and the possibility of autoclave corrosion could limit the industrial application.

A new and highly efficient catalytic system ($Pd(OAc)_2$/dppp/$CO/H^+$) has been developed for the synthesis of *gem*-$\alpha,\beta$-unsaturated amides. The selectivity is more of electronic than steric effect; the change of the ligand from dppp [1,3-bis (diphenylphosphino) propane] to dppb [1,4-bis (diphenylphosphino) butane] and the use of $H_2$ in place of acid inverse the regiochemistry of the reaction to yield *trans*-$\alpha,\beta$-unsaturated amides. This inversion has been attributed to the steric effect of the ligand and substrates. Also for the first time cyclic substituted imides has been synthesis by the direct carbonylative of terminal alkynes with aniline derivatives. Similarly, internal alkynes were also carbonylated to disubstituted amides with lower selectivity.

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# خلاصة الرسالة

الأســـــم : جيمو تيجاني
عنوان الرسالة : تفعلات الاختيار الفراغي الكربونيل لإزدواج الامكانيات مع مشتقات الانيلين والمحفزة بالبالاد يوم
التخصص : كيماء
التاريخ : مايو ٢٠٠١

إن تفاعلات carbonylation تعتبر من أهم التحولات التي يتم تحفيزها بمتراكبات العناصر الإنتقالية . وهي طريقة ذات كفاءة عالية في إدخال مجموعة كربونيل على مركب عضوي . فالإزدواج المباشر لمجموعة الكربونيل للأمكانيات والأمينات ينتج أميدات غير مشبعة وبالإضافة لذلك مركبات عالية السُمية مثل Ni(CO)4 وهاليرات النيكـــــل و 4 ( Ni( CN و 4 ( Ni( CO كانت تستخدم ولكن نشاطها الضعيف أدى إلى إستخدام ظروف تفاعل صعبة .

تم تطوير عامل حفاز جديد هو ( Pd(Oac)2/dppp/CO/H+ ) ذو كفاءة في تحضير جسيم ، ألفا ، بيتا - أميدات غير مشبعة . وجد أن الاختيارية في التفاعلات بسبب الطبيعة الالكترونية وليـــس نتيجـــة الشـــغل الفراغـــي ؟ تغـــير اليجـــاند مـــن ( dppp[1,3- (bis(diphosphino)propane إلى ( dppb[1,4- bis(diphenylphosphino)butane) واستخدام الهيدروجين بدلاً من الحمض يعكس الكيمياء الفراغية للتفاعل وينتج فرانس ؟ ألفا ؟ بيتا - أميدات غير مشبعة . هذا الانعكاس يعزي إلى تأثير الحجم الفراغي لليجاند والمتفاعلات . وأيضا للمرة الأولى يتم إنتاج إميدات حلقية بالتفاعل المباشر للأمكانيات الطرفية مع مشتقات الأنيلين وبنفس الطريقة تم إدخال مجموعة الكربونيل على مركبات الأمكانيات الداخلية لإنتاج أميدات ثنائية المجموعات بإختيارية أقل .

درجة الماجستير في العلوم
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مايو ٢٠٠١

# CHAPTER 1

## INTRODUCTION AND LITERETURE OVERVIEW

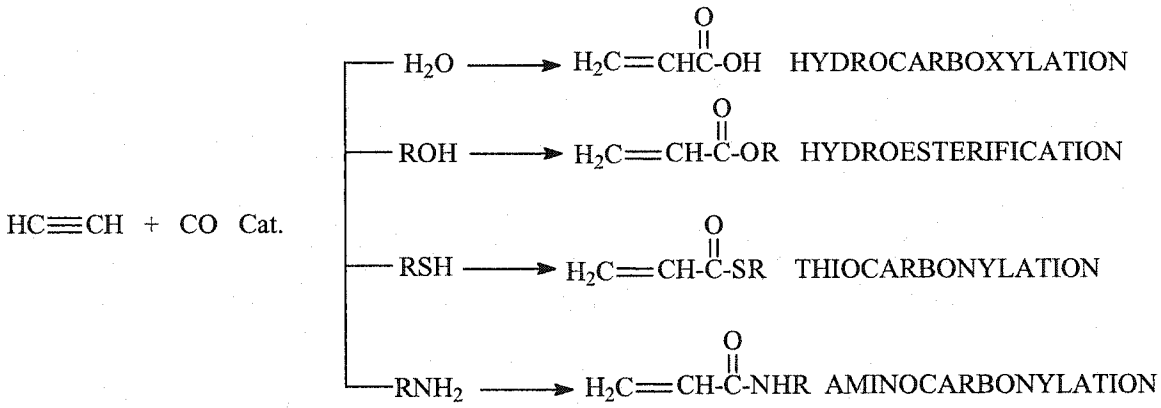
### 1.1 Introduction

The term "carbonylation" was coined by W. Reppe during the thirties and is generally used to refer to those reactions in which CO alone or CO combined with other compounds (especially nucleophiles with mobile H-atom) are introduced into particular substrates (saturated or unsaturated) [(1)]. 'Carbonylation' is used here as a generic term, including reactions such as formylation, hydroformylation, carboxylation, and homologation, all involving the introduction of a carbonyl group into an organic substrate. Group VIIIB metals, especially Fe, Co, Ni, in the form of metal carbonyls or other derivatives, which, under reaction conditions are transformed into carbonyls, catalyze these reactions. More recently Ir, Rh, Ru, Os, Pt, and Pd complexes have been widely used as catalysts [(1,2)].

Carbonylation reactions rank among the most useful transformations homogeneously catalyzed by transition-metal complexes, forming the basis for industrial and laboratory processes currently in practice [(3)]. Some of the initial scientific discoveries in this field gradually evolved into large-scale commercial carbonylation processes. Noteworthy among the commercial carbonylation processes are the 'oxo' process (olefin hydroformylation), the Reppe process (hydrocarboxylation of acetylene to acrylic acid) and Monsanto process (carbonylation of methanol to acetic acid) [(3,4,5)]. These processes are employed worldwide to prepare millions of tones of commodity chemicals each year.

In addition, it has been predicted that the important of carbonylation reactions in the total chemical out put will continue to grow as several new carbonylation processes are expected to reach commercialization soon. The basic reason is that the feedstock i.e. syngas (carbon monoxide & hydrogen) are versatile and inexpensive [4].

The carbonylation of alkenes and alkynes with CO and water is known as hydrocarboxylation reaction. If alcohol is used in place of water it is referred to as hydroesterification. While addition of CO and amines or CO and thiols to unsaturated compounds are referred to as aminocarbonylation and thiocarbonylation respectively [1] (scheme 1).




Scheme 1

## 1.2 Literature overview

### 1.2.1 Carbonylation of Alkenes

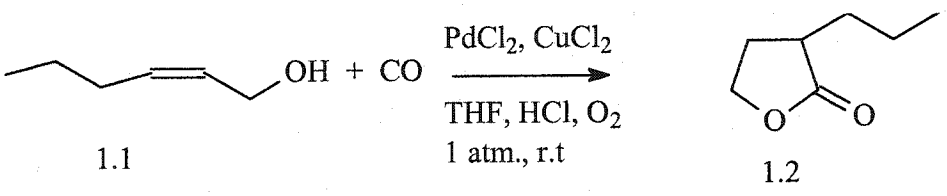
The synthesis of carboxylic acids or their ester derivatives, by the reaction of an olefinic substrate with CO and water or alcohol, catalyzed by phosphoric acid or other Lewis acids has been known, since 1931 [6]; branched aliphatic acids and esters are obtained. In the presence of $H_2SO_4$, the reaction may be carried out under milder

condition [7]. This synthesis, however, has a serious limitation due to the experimental conditions and the complex mixture of products. Much more interesting, is the carbonylation of olefinic substrates conducted in the presence of metal carbonyls or metal compounds which under the reaction conditions may be transformed into metal complexes containing carbonyls groups. This reaction, discovered by Reppe and Kroper around 1940 [8,9], consists of the addition of hydrogen and carboxylakyl, thiocarboxyalkyl, amide, or similar group to an olefinic substrate (eq. 1.1).

$$R^1CH{=}CH_2 + CO + HOR^2 \xrightarrow[\text{Solvent, } t^oC]{\text{Cat., Ligand}} R^1CH_2CH_2CO_2R^2 + R^1CH(CH_3)CO_2R^2 \qquad \text{eq. 1.1}$$

$R^1$ = alkyl or aryl  $R^2$ = H or alkyl or aryl

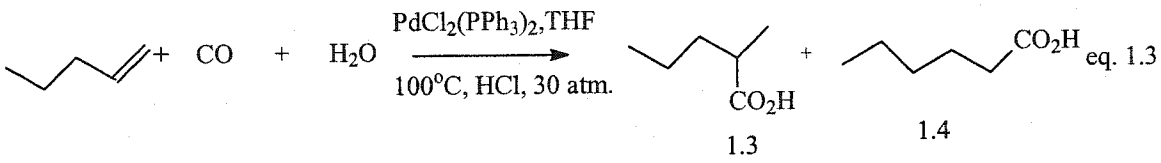
The standard carbonylation catalysts such as $Co_2(CO)_8$ and $Ni(CO)_4$ have been used to prepare fatty-acid esters [10]. More recently, other catalysts based on Pd, Pt, Rh, and Ru found widespread use because of their better performance under milder reaction conditions [1,11]. Molecules containing both olefinic unsaturations at suitable distance, and a group having active hydrogen (**1.1**) may react with CO to give cyclic compounds (**1.2**) [12,13,14] (eq. 1.2).



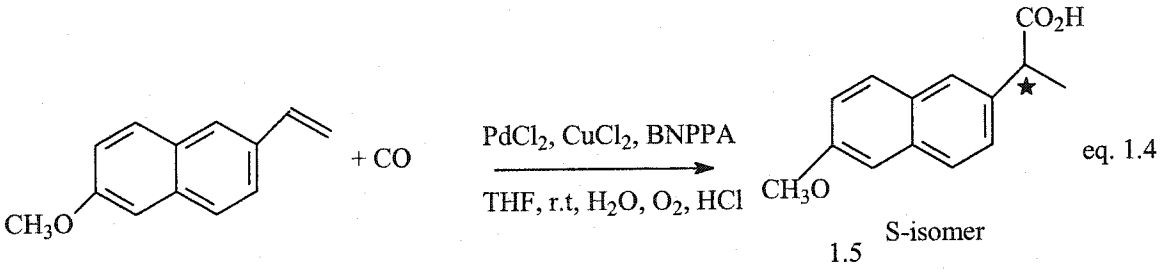

1.1 1.2 eq. 1.2

The regioselectivity of linear versus branched products is an important issue, because mixtures of isomeric carboxylic acids or esters are usually obtained, owing to Markovnikov and anti-Markovnikov addition of the metal hydride to the alkene. In fatty

acids synthesis linear isomer is preferred [10] **(1.4)** (eq. 1.3), whereas the converse is the case in carbonylation of pro-chiral styrene related compounds to give chiral arylpropionic acids **(1.5)**, an important class of non-steroidal anti-inflammatory agents [15,16,17,18]. The regioselectivity in palladium-catalyzed reactions, involving phosphine ligands, are largely controlled by the variation of the ligands (eq. 1.3). $PPh_3$ promotes preferential carbonylation of alkenes toward the branched acid **(1.3)**, whereas bidentate phosphine ligands give linear products **(1.4)** overwhelmingly [19,20,21,22].




The steric and electronic effects of the chiral phosphine ligands exert a dramatic influence on the yield and selectivity of the reaction. In fact, the hydrocarboxylation reaction of 6-methoxynaphthalene under mild experimental conditions in the presence of (S)-(+)-binaphthyl-2,2'-diyl hydrogen phosphate (BNPPA) gave optically active naproxen **(1.5)** (72-91% ee) in good chemical yields (46-71 %) (eq. 1.4) [17,23].




The development of two-phase catalysis processes where the catalyst can be separated from the products and recycled is an important step toward economical and

friendly environmental processes. For example, the catalytic system composed of water-soluble triphenylphosphine trisulfonate (TPPTS), Pd complex as catalyst, and acid as a promoter [24] gave very high yield and selectivity of carboxylic acids (eq. 1.5).

$$CH_3(CH_2)_3CH{=}CH_2 + CO + H_2O \xrightarrow[HCl,\ 100^{\circ}C,\ 50\ bars]{PdCl_2,\ TPPTS,\ THF} CH_3(CH_2)_5CO_2H + CH_3(CH_2)_3CH(CH)_3CO_2H \quad \text{eq. 1.5}$$

### 1.2.2 Carbonylation of Alkynes

The high reactivity of the acetylenic compounds with CO in the presence of transition metals, particularly group VIII, including the great industrial importance of the products obtained, led to a significant scientific and industrial activity in this field since these discoveries. The scope of the reaction of the carbonylation of alkynes was extended to obtain a large variety of derivatives of mono- and dicarboxylic acids, keto acids, esters of aldehydo-acids, cyclic ketenes and hydroquinones [2].

The first research on addition of CO to acetylene in the presence of transition metal compounds or metal carbonyls was carried out in Germany between 1938 and 1940 by two different industrial research groups, working under the supervision of Reppe [25] and Roelen [26]. Reppe was investigating new aspects of acetylene chemistry when he reacted acetylene with $Ni(CO)_4$ and water (eq. 1.6) and obtained acrylic acid (eq. 1.7) instead of the expected aldehydes. Roelen was investigating the hydroformylation of olefins in the presence of cobalt catalysts and as a logical extension he tried to carry out the hydroformylation of acetylene. He obtained, however, high-molecular-weight products containing only traces of acrolein, the expected product [25,26].

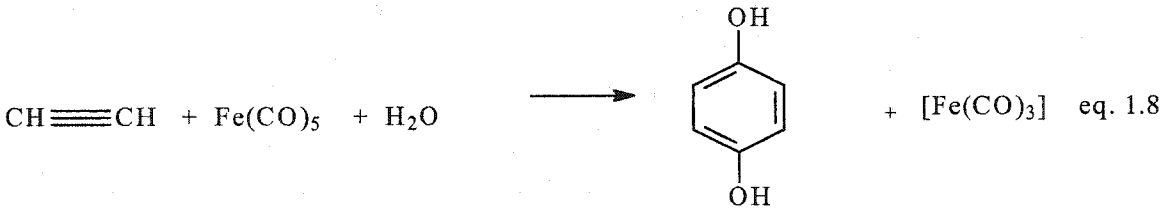
$$CH{\equiv}CH + CO \xrightarrow{Ni(CO)_4} CH{\equiv}CH{-}CHO \qquad \text{eq. 1.6}$$

$$CH{\equiv}CH + CO \xrightarrow[H_2O]{Ni(CO)_4} CH_2{=}CHCO_2H \qquad \text{eq. 1.7}$$

The most widely used catalysts for commercial alkynes carbonylation were the $Ni(CO)_4$ and $Co_2(CO)_8$, or their precursors. In general, these catalytic systems require high temperature (100-200°C) and pressure (30-200 atm); milder conditions (25-100°C, 1-10 atm) usually were used in stoichiometric reactions [27]. Attempts to decrease the $Ni(CO)_4$ consumption have led to "semi-catalytic" processes in which CO gas was used in addition to the $Ni(CO)_4$ [2]. An important disadvantage of using this catalyst was the formation of the volatile $Ni(CO)_4$ during the reaction. $PPh_3$ ligand, have been used to counteract this problem [28], but the presence of the ligand reduced the catalytic activity.

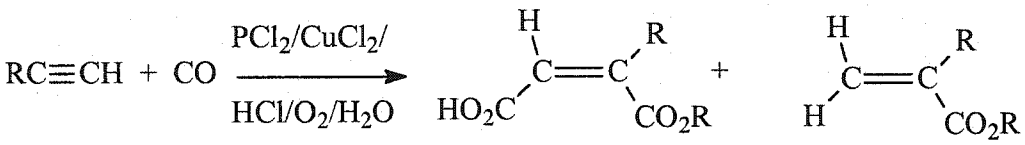
Other cobalt compounds were used in the stoichiometric and catalytic carbonylation of alkynes under milder conditions. In general, however, the stoichiometric carbonylation of alkynes with $Co_2(CO)_8$ and $HCo(CO)_4$ is rather unsuccessful, because these compounds form very stable and unreactive complexes with alkynes [2]. In contrast, under more severe conditions (100-200°C, 200-300 atm. of CO), cobalt compounds show high catalytic activity for alkynes carbonylation.

The reactivity of iron, ruthenium, rhodium and osmium have not yet been investigated systematically, but the existing reports indicate that products such as quinines, hydroquinones (eq. 1.8) and lactones are formed, in the reactions of these metals with alkynes. In general, the catalytic reactions are sluggish and the product distributions are poor [2].




eq. 1.8

The use of palladium-catalysts in alkynes carbonylation was first reported in 1962 [29,30]. Tsuji and co-worker were the first to study the carbonylation of alkynes with palladium complexes involving the catalytic system $PdCl_2/CuCl_2/HCl/O_2$ to produce mainly products of dicarbonylation (eq. 1.9) [31,32,33,34,35].



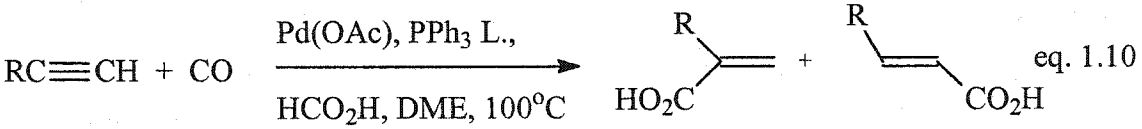

eq. 1.9

R = alkyl or aryl

### 1.2.2.1 Hydrocarboxylation of alkynes

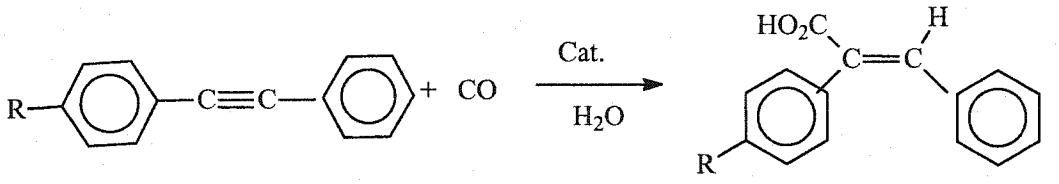
The synthesis of α,β-unsaturated acids is one of the most important of the acetylene carbonylation reactions and it has found practical application in laboratory and industrial scale. Unsubstituted and substituted acrylic and succinic acids are the main products prepared from acetylenic substrates, CO, and water; moreover, other mono- and polycarboxylic acids were obtained in smaller amount [25,26]. The reactions can be carried out either at 90-200°C under CO pressure (30-200 atm.) in the presence of metal carbonyl (group VIII), or milder conditions with stoichiometric amount of $Ni(CO)_4$ [2]. Most of the hydrocarboxylation reactions were carried out in acidic medium; however, Sternberg and coworkers reported the hydrocarboxylation of diphenylacetylene in alkaline medium

using $Ni(CO)_4$ [36]. Alkynes are hydrocarboxylated with formic acid in the presence of $Pd(OAc)_2$ and suitable phosphine ligand to give both linear and branched unsaturated carboxylic acids (eq. 1.10); The regioselectivity is in favor of the branched.




eq. 1.10

In hydrocarboxylation of substituted diphenylacetylene, electron-donating substituents (methoxy, methyl, etc) in para-position favored the carbonylation of the acetylenic carbon atom adjacent to the para-substituent (eq. 1.11), opposite behavior was observed with electron-withdrawing groups (Cl, $NO_2$, etc). The presence of a substituent in the ortho-position induces carbonylation of the carbon adjacent to the substituted phenyl group [1,3,4,5,37].




eq. 1.11

Anomalous results occur when hydrogen of the acetylenic carbon is replaced by a halogen **(1.6)** and propargylic halides **(1.7)**. The former gave hydrocarbons (eq. 1.12), whereas the later gave allenic acids **(1.8)** (eq. 1.13) [38]. Cylocarbonylation of unsaturated alcohols, amines, and other suitable substrates, produce lactones, lactams or other cyclic compounds [39].

$$2CH_3C{\equiv}CI + 2Ni(CO)_4 + 2AcOH \longrightarrow 2CH_3C{\equiv}CH + NiI_2 + Ni(OAc)_2 + 8CO \quad \text{eq. 1.12}$$

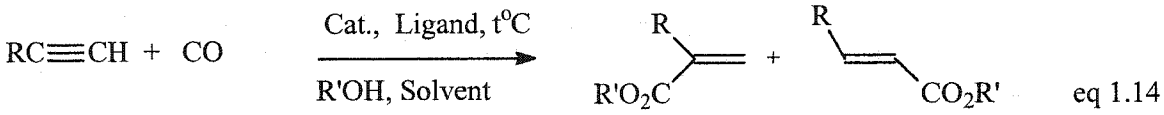
1.6

$$HC{\equiv}CCH_2Cl + H_2O \xrightarrow[-HCl]{Ni(CO)_4} CH_2{=}C{=}CHCOOH \quad \text{eq. 1.13}$$

1.7 1.8

### 1.2.2.2 Hydroesterification of Alkynes

The transition-metal catalyzed carbonylation of alkynes known since the pioneering work of Reppe, has been optimized for nickel carbonyls and variety of cobalt and iron carbonyl. Platinum complexes needed $SnCl_2$ as a promoter. Palladium-catalyzed hydroesterification of 1-alkynes normally gives rise to linear and branched $\alpha,\beta$-unsaturated esters. The ratio depends on the reaction condition employed [40] (eq. 1.14).



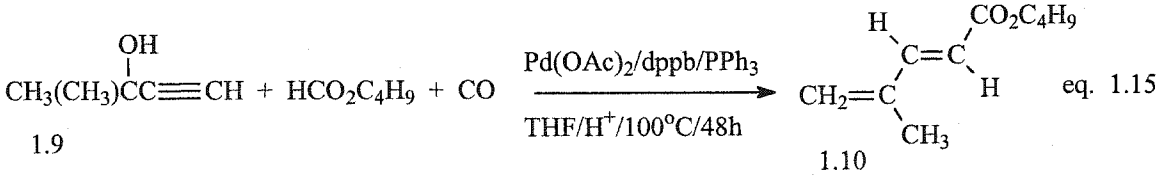

eq 1.14

R' = aryl, Ph, alkyl. Pd = $Pd(PPh_3)_4$ or $Pd(OAc)_2$/dppf

Usually, the regioselectivity for the formation of branched (acrylates) has been observed with the system comprising of palladium black and HI in the hydroesterification of phenylacetylene and propyne to afford the branched esters selectively [41]. Similarly, the regioselective hydroesterification of terminal alkynes catalyzed by $Pd(dba)_2$/dppb gives branched esters [42], the reaction occurred well even with tertiary alcohols. Aryl- and alkyl-acetylenes are carbonylated in the presence of $Pd(PPh_3)_4$ or $Pd(OAc)_2$/dppf using phenol as nucleophile to give branched esters in good selectivity and yield [43].

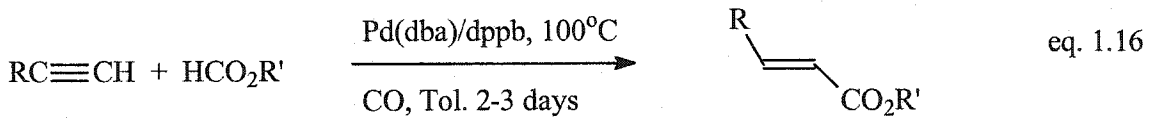
The hydroesterification of terminal alkynes with butanol by the catalytic system $Pd(dba)_2/PPh_3$/*p*-TsOH also proceeds smoothly under the normal pressure of CO to afford

branched esters selectively [44]. The regioselective hydroesterification of alkynes and alkynols **(1.9)** using formate esters catalyzed by $Pd(OAc)_2$/dppb/ $PPh_3$/P-TsOH have been reported [45] (eq. 1.15). $Pd(OAc)_2/PPh_2Py/MeSO_3H$ gives very active system, which catalyzes the hydroesterification of propyne with excellent selectivity toward branched ester (99.95%) [46].




1.9 1.10 eq. 1.15

On the other hand, different catalytic systems capable of giving selectively the linear esters have been reported. For instance, Knifton reported the monophosphine-stabilized Pd(II)/Sn(II) system which catalyzed the hydroesterification of 1-heptyne at 80°C and 240 atm with 81% selectivity for the linear ester and 65% combined yield [47]. Thus, $Pd(dba)_2$/dppb catalyzed the regioselective conversion of terminal alkynes and formate esters into linear $\alpha,\beta$-unsaturated esters (eq. 1.16) at 100°C under CO pressure of 80 atm [48].

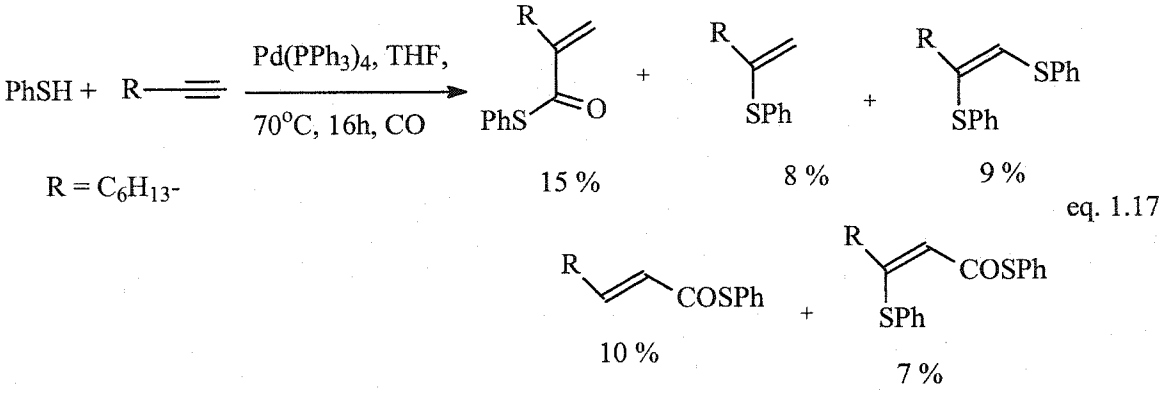



eq. 1.16

Similarly, $PtCl_2$(dppb) with $SnCl_2$ as promoter were reported to the give linear isomer as major product, however, the chemoselectivity of the reaction was poor due to the formation of high molecular mass by-products, and to partial polymerization of both substrate and carbonylation product [49].

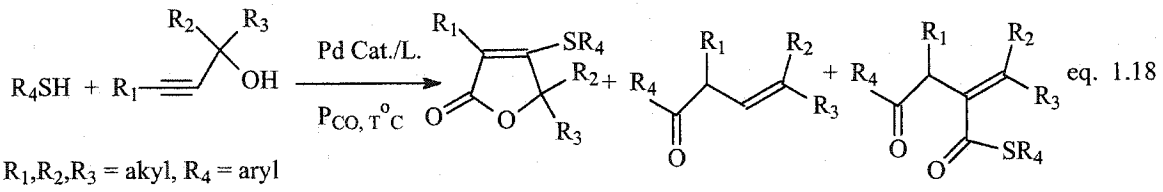
### 1.2.2.3 Thiocarbonylation of alkynes

The transition-metal-catalyzed carbonylation of organic sulfur compounds has been the subject of few investigations [50]. It was previously considered that many transition metals, including palladium, have strong affinity to thiols, which make the catalytic reactions ineffective. A series of transition-metal-catalyzed addition and carbonylation- addition reactions of organic disulfides and thiols to acetylenes has been developed [51]; $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ gave a complex mixture of products (eq. 1.17) in carbonylative addition of thiophenol with 1-octyne [52].




eq. 1.17

$Pt(PPh_3)_4$ gave predominately branched isomer thioester *via* carbonylation acetylene with benzothiol [53]. Recently, Alper and coworkers have introduced new interesting methods of palladium-catalyzed thiocarbonylation of propargylic alcohols [54] (eq. 1.18), allylic alcohols [55], allenes [56], and enynes [57].




eq. 1.18

### 1.2.2.4 Aminocarbonylation of Alkynes

Reppe was the first to synthesize substituted acrylamides from acetylene and various amines in the presence of $Ni(CO)_4$. He prepared many acrylamides by reacting acetylene or phenylacetylene with carbon monoxide in the presence of primary or secondary amines, aniline, urea, pyrolidone or acetamide. Stoichiometric quantities of $Ni(CO)_4$ were employed along with polymerization inhibitors such as hydroquinine [58]. Similarly, the use of nickel halides as catalyst has also been reported in xylene or benzene as solvent at 100-190°C to give isolated yield of amide ranging between 20-50% [59] (eq. 1.19).

$$RNH_2 + HC{\equiv}CH + CO \xrightarrow[HCl,\ 150^{\circ}C]{Ni\ Cat.,C_6H_6} CH_2{=}CHCONHR \qquad \text{eq. 1.19}$$

Naher et al. reported in 1956 the first semi-catalytic synthesis of acrylamides. They reacted acetylene and $Ni(CO)_4$ in acrylic acid and then successively added CO, HCl, and excess ammonia, at 50-90°C [60]. The highest yields were obtained with aniline and secondary amines; however, with primary amines, secondary reactions sometimes occurred to yield bisacryloylamines (eq.1.20).

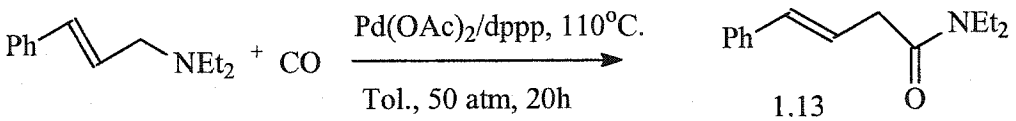
$$CH_2{=}CHCONHR + HC{\equiv}CH + CO \xrightarrow[HCl,\ T^{\circ}C]{Ni\ Cat.,C_6H_6} \begin{matrix} CH_2{=}CHCO \\ \diagdown \\ NR \\ \diagup \\ CH_2{=}CHCO \end{matrix} \qquad \text{eq. 1.20}$$

Acetylene reacted with diethylamine to form succinic acid and diethyl acrylamide with 12% and 66% yield respectively by using $Ni(CN)_2$ catalyst. $Co_2(CO)_8$ was found to catalyze the reaction of aniline, CO and acetylene to giving succinic acid dianiline **(1.11)** [61] (eq. 1.21).

$$CH{\equiv}CH + 2PhNH_2 + 2CO \xrightarrow[\text{Tol. t°C}]{Co_2(CO)_8} PhNHCOCH_2CH_2CONHPh \quad \text{eq. 1.21}$$

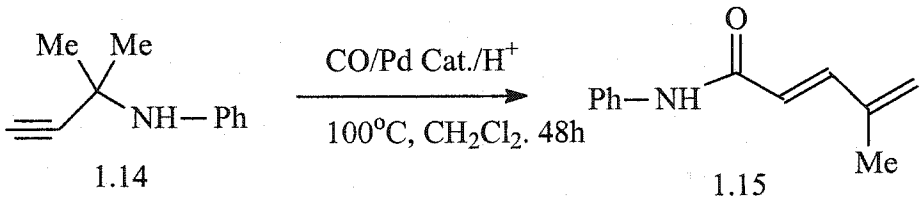
1.11

Palladium-complexes were also used in the synthesis of 2-substituted acrylamides *via* carbonylation of various terminal alkynes with diethyl amine in the presence of organic iodides or HI salt [62]. Similarly, palladium-catalyzed carbonylation of allylamines **(1.12)** under CO (50 atm) at 110°C proceeded efficiently to give the corresponding $\beta,\gamma$-unsaturated amides **(1.13)**. The carbonylation occurred at the less substituted carbon of the allyl units to give linear amides with high regioselectivity [63] (eq. 1.22).




1.13 eq. 1.22

Recently, the selective synthesis of $\alpha,\beta$-unsaturated amides **(1.15)** has been achieved via palladium (0)-catalyzed insertion of carbon monoxide into an unactivated carbon-nitrogen bond of propargylamines [64] **(1.14)** (eq. 1.23) and 2,3- dienylamines [65].

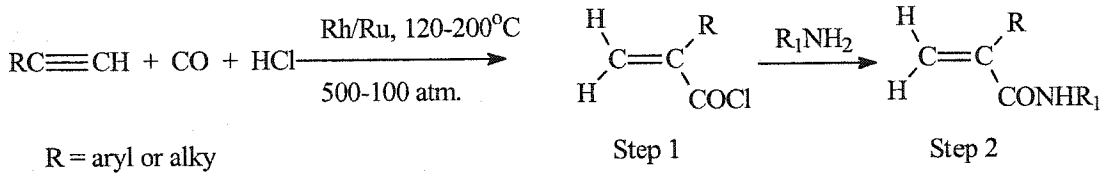



1.14 1.15 eq 1.23

## 1.3 Conventional methods for the synthesis of unsaturated amides

The classical synthesis of 2-substituted acrylamides, important intermediates for polymer synthesis [66], was mostly achieved by reacting substituted amines (or derivatives

of aniline or acrylonitriles) [67] with acryloyl chlorides or substituted acrylic acids [68] (Scheme 2).




Scheme 2

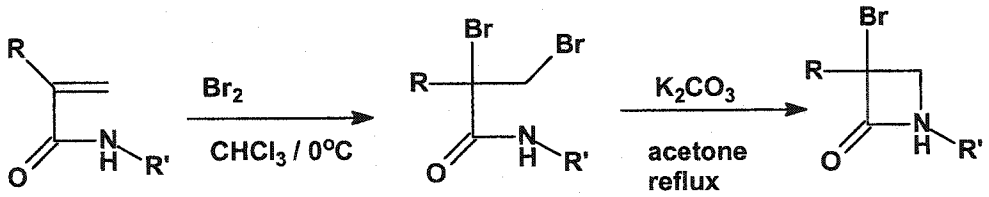
While $\alpha,\beta$-unsaturated amides could be synthesized by the olifination of aldehyde with carbamidomethylene triphenylphosphorane **(1.16)** [69] (eq. 1.24).

$$\underset{}{PhCOH} + \underset{\mathbf{1.16}}{Ph_3P{=}CHCONH_2} \longrightarrow \underset{\mathbf{1.17}}{PhCH{=}CHCONH_2} + Ph_3PO \qquad \text{eq. 1.24}$$

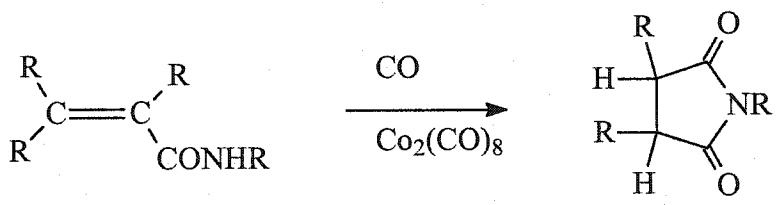
## 1.4 Uses and importance of unsaturated amides

The principal application of acrylamides is in the synthesis of water-soluble polymers, used as additives for water treatment, to enhance oil recovery (to control fluid loses), as flocculants, as papermaking aids (used as binder and retention aids for fibers and papers), as thickeners (formulated in cosmetics, soaps, hair grooming, and pre-shave lotions preparation) [70]. Acrylamides are also used as soil conditioning agents, and in sewage and waste treatment (to remove suspended solid in industrial waste water before discharge, reused or disposal). Acrylamides are also applied in ore processing, in the synthesis of dyes, and copolymer in the production of contact lenses, resins, emulsion stabilizers for printing ink, gelling agents for explosives, binders in adhesives and adhesives tape, and gel chromatography and electrophoresis [71].

2-Substituted acrylamides can also be used in the synthesis of $\beta$-lactams, which represent an important class of antibiotics [72] (Scheme 3). $\alpha,\beta$-Unsaturated amides are also important precursors for the synthesis of cyclic compounds such as 2-oxindoles [75], imides [14] (eq. 1.25) and jatrophams [74] etc.




**Scheme 3**




eq. 1.25

## 1.5 Conclusion

The analysis of the literature data on carbonylation of alkynes shows that these reactions provide convenient, efficient and one step methods for the synthesis of unsaturated acids and derivatives. Among the group VIII transition metal used, $Pd(OAc)_2$/phosphine ligands gave excellent results under mild conditions.

## 1.6 Objectives

All the methods used in the synthesis of $\alpha,\beta$-unsaturated amides have limitations, which are related to the availability and / or to the low reactivity of the starting material. In addition, the conventional synthesis of unsaturated amides required many steps and the

yields were not high. Therefore, one-step catalytic synthesis of $\alpha,\beta$-unsaturated amides from readily available starting materials, under mild reaction conditions represents an important task in chemistry. The importance of the products and yet the lack of a catalytic method urged us to set the following objectives:

1. To develop a new synthetic method for the synthesis of these industrially important compounds.

2. To study the possibility of the carbonylation of aniline derivatives with aliphatic and aromatic alkynes (terminal and internal).

3. To determine the reaction conditions (regarding the type of catalyst, co-catalyst, ligand, acidity, temperature, pressure, solvent and reaction time etc) that will control the selectivity toward *gem*-$\alpha,\beta$-unsaturated amides or *trans*-$\alpha,\beta$-unsaturated amides.

4. Catalytic synthesis of new gem and *trans*-$\alpha,\beta$-unsaturated amides.

5. Separation of isomers.

6. To identify and to determine the yield and the selectivity of the products of each reaction by using: G.C, G.C-M.S, FT-IR, elemental analysis, $^{1}H$ and $^{13}C$ NMR.

# CHAPTER 2

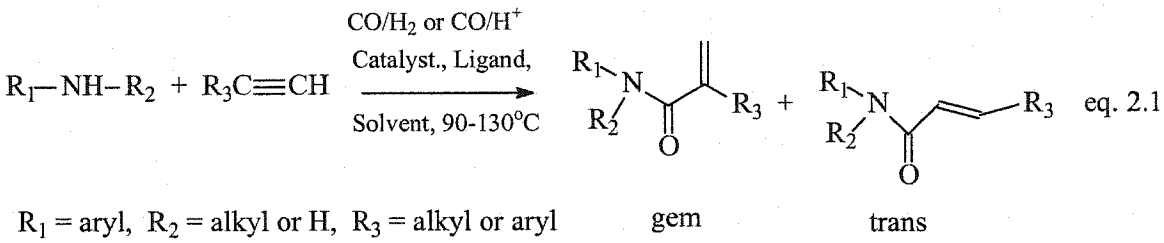
## TRANSITION METAL CATALYZED CARBONYLATIVE COUPLING OF ALKYNES WITH ANILINE DERIVATIVES INTO *GEM*-$\alpha,\beta$-UNSATURATED AMIDES (2-SUBSTITUTED ACRYLAMIDES)

### 2.1 Introduction

Carbonylation with transition-metal complexes represents an efficient method for the direct introduction of the carbonyl moiety into organic molecules [1-5,8,9]. Direct carbonylative coupling of alkynes with amines yield $\alpha,\beta$-unsaturated amides [1-5,58,62]. Highly toxic $Ni(CO)_4$ was the first catalyst used in carbonylation of acetylene, later nickel halides, $Ni(CN)_4$ and $Co_2(CO)_8$ were also used but their activities were very low and therefore they required severe reaction conditions. Aminocarbonylation of terminal alkynes proceeded regioselectively in the presence of palladium complexes and iodide [62] as a promoters, contamination by the volatile iodine compounds [5] and the possibility of autoclave corrosion could limit the industrial application.

Palladium-catalyzed carbonylation of 1-alkynes (addition of H-CONHR across acetylenic linkage) gives branched (*gem*)-$\alpha,\beta$-unsaturated amides, if the hydride (H-) is bonded to terminal carbon and the amide (-CONHR) is bonded to the internal carbon i.e. Markovnikov addition. The reversed reaction (anti-Markovnikov addition) yields linear *(trans)*-$\alpha,\beta$-unsaturated amides (eq. 2.1). The regioselectivity depends on the reaction conditions employed. How these conditions affect the yield and regiochemistry of the reactions? To answer this question, a systematic study of catalytic carbonylative coupling

of terminal alkynes with aniline derivatives were performed using $Pd(OAc)_2$/dppp/$CO/H^+$ (Section 2.2-2.2.11).




## 2.2 Results and discussion

The synthesis of *gem*-$\alpha,\beta$-unsaturated amides (acrylamides) was performed by the direct carbonylation of terminal alkynes to aniline derivatives, under CO pressure in the presence of acid and transition metal catalyst. In this system, $Pd(OAc)_2$, *p*-TsOH, and ligands were added separately to the reaction mixture and the active catalytic complex was generated *in situ* [75]. To determine the most suitable reaction conditions, 1-heptyne and aniline was used as the model substrates. The choice of aniline and 1-heptyne are based on high their reactivity [2].

### 2.2.1 Effect of phosphine ligands

The introduction of phosphine ligand along with transition-metal complexes played a key role in the carbonylation of alkynes. The presence of the ligand stabilizes the active catalytic intermediate of the reaction. The absence of these coordinating ligands resulted in the precipitation of palladium as finely divided metal [76]. The influence of ligand on the yield and the selectivity of the reaction were carefully investigated. The

carbonylation of 1-heptyne with aniline was first carried out in the presence of the following co-catalyst: $Ph_3Bi$, $Ph_3Sb$, $Ph_3As$, $Ph_3P$, $(o\text{-}CH_3C_6H_5)_3P$ and $(C_6H_{11})_3P$. The first four ligands have different donor atoms and their electron donating ability is in the following order: $Ph_3Bi < Ph_3Sb < Ph_3As < Ph_3P$ [77], whereas the last three have the same center atom, but different basicity and cone angles (the order of basicity and cone angle are: $(C_6H_{11})_3P > o\text{-}CH_3C_6H_5)_3P > Ph_3P$ and $(o\text{-}CH_3C_6H_5)_3P$ (194°) > $(C_6H_{11})_3P$ (179°) > $Ph_3P$ (145°) respectively [78]). Among all these co-catalysts, only $PPh_3$ with moderate basicity and least cone angle poorly promote carbonylation of 1-heptyne (yield 26% and 83:17 ratio (*gem: trans*), all the others gave only traces. Earlier reports [79,80] on olefins carbonylation also show similar results.

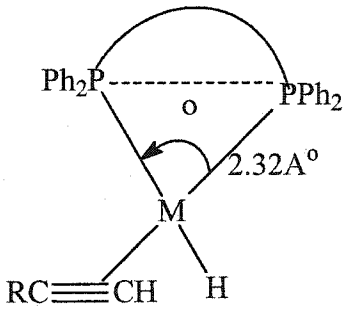
The *gem*-isomer **(β-4.3)** *N*-Phenyl-2-pentyl propeneamide can easily be distinguished from the *trans*-isomer **(α-9.3)** *N*-Phenyl-2-octeneamide in a $^1H$ NMR 500 MHz by the presence of two sharp singlets at 5.36 ppm and 5.68 ppm belonging to the two *geminal* hydrogen's, whereas the *trans* has a doublet at 5.91-5.94 ppm (J = 15.25 Hz) and quintet at 6.29-6.95 ppm for the olefinic hydrogen's.

Similarly, different bidentate ligands were tested. The most effective bidentate ligand in term of both yield and selectivity is dppp, as shown in Figure 2.1 and 2.2. The shorter chain congener, dppe was found to be lower in effectiveness in term of yield, though it produced the highest selectivity toward *gem-α,β*-unsaturated amides **(2.1)**. Dppm have little or no activity under the same conditions. While the longer chain, dppb gave an acceptable yield and selectivity of 59% and 78%; dpppt gave much lower yield (23%) and slightly higher selectivity (82%). Binap (2,2'-bis(diphenylphosphino)-1,'-

binaphthyl) with bite angle close to that of dppp gave slightly higher selectivity but lower isolated yield due to significant side product (15% coupling without CO insertion).

The natural bite angle is defined as the preferred chelation angle determined only by ligand backbone constraints and not by metal valence angle. While the flexibility range is defined as the accessible range of bite angles, within <3 kcal $mol^{-1}$ excess strain energy, from the calculated natural bite angle [81]. The calculation of ligand bite angles is done by either molecular modeling or P....P distances determined from crystal structure can be used. Molecular modeling has been used to calculate "natural" bite angles using "rhodium" dummy atom and fixed Rh-P distances of 2.32 $A^o$ [81] (Figure 2.1).

A correlation between diphosphine ligand bite angle, rate and selectivity has been observed. Dppe with the bite angle of 85° gave 6% as yield and 100% selectivity, while dppp and binap with bite angles 91° and 92° produced 95% and 81% yield with selectivity of 94% and 98% respectively. Further increase in the bite angle to 98° and 102° in dppb and dpppt reduces the yield to 59% and 23% and selectivity to 78% and 82% respectively.

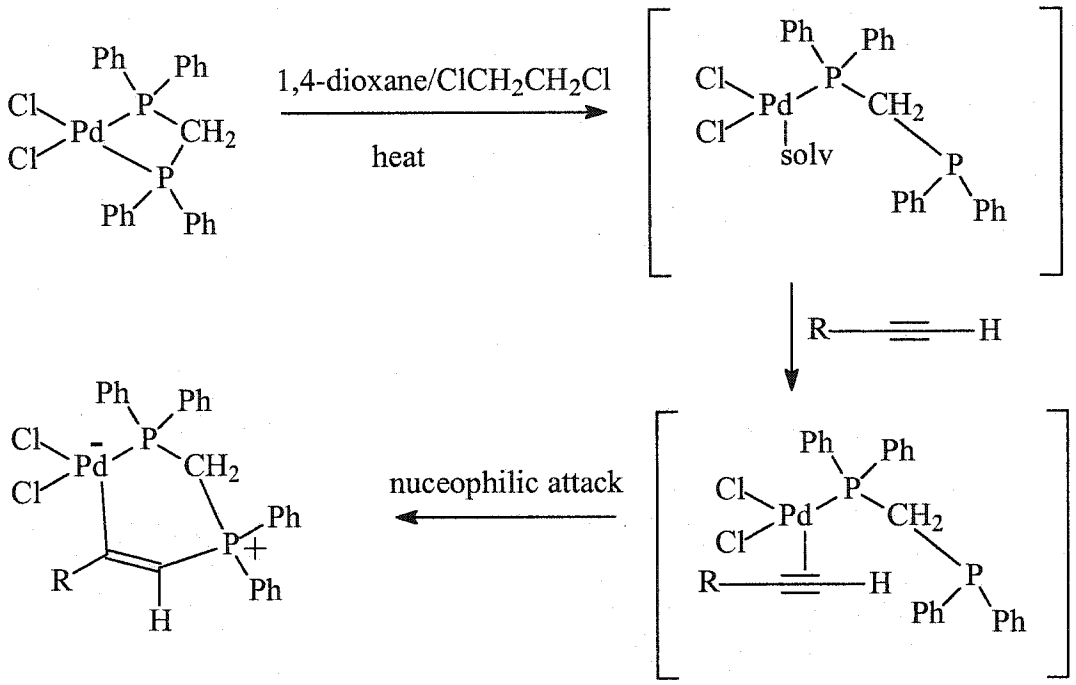



Angle = 2arcsin1/2(p...p)/2.32A°

M = Pd or other metal

**Figure 2.1** Schematic representation of bite angle of a bidentate ligand

The probably reason for the poor yield of dppm may be because of its chelation to give unstable four-membered ring cyclic ligand-metal complex, which formed thermodynamically stable palladium alkenyl phosphorous ylide by insertion of alkyne into palladium-phosphine bond [82] (Scheme 4).




Scheme 4

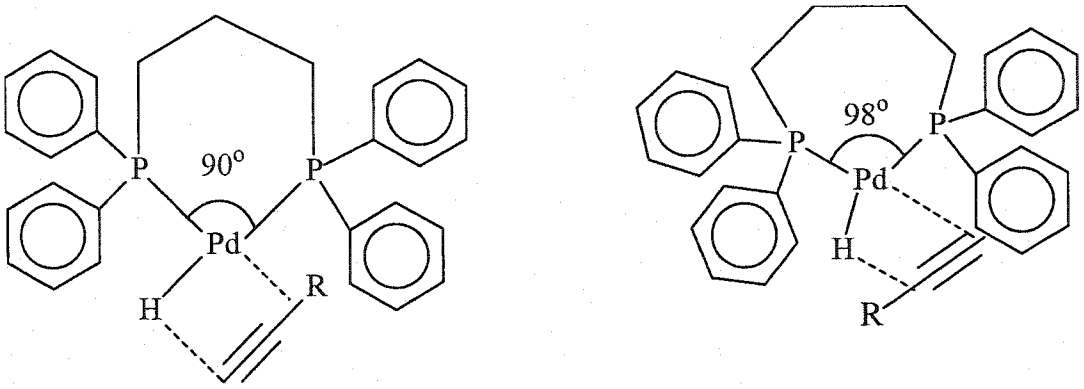
When we consider the flexibility of the bidentate ligands dppe, dppp and dppb coordinated to one metal center, it may be seen that for dppp and dppb the organic backbone is bent out of the plane of coordination and that in contrast, a skew conformation observed for dppe. In dppp and dppb complexes the phenyl groups can bend away from the remaining two coordination sites [83,84]. Flexible backbones also impose

low-energy barriers for the variation of the P-Pd-P angle and Pd-P distances. Moreover, theoretical calculations [85,86] indicate such flexibility may enhance migration reactions.

The lower reactivity of dppb compared to dppp metal complex is ascribed to the *trans* configuration of its oligomeric acyl complex, (phenomenon which is not observed in neutral complex [83]). About half of the complex occurs in *trans* configuration in ionic dppb complex. The decrease in the rate of carbonylation for *trans* complex would be expected, since there is neither a CO in a *cis* to the coordinated alkenyl ligand as would required for a *cis* migration processes nor there is a phosphine *trans* to the Pd-alkenyl that can activate the migrating alkenyl group [83]. A similar lower yield and selectivity of 1,5-bis(diphenylphosphino)pentane (dpppt) may also be connected to the *trans* effect with has been previously observed when *n* is equal to 6, 8, 10 and 12 ($Ph_2P(CH_2)_nPPh_2$) [84,87].

The fact that dppp and binap have a very similar bite angle (~90°) and both gave an excellent yield and selectivity of *gem*-isomer could lead us to suggest that the transition state complex is probably a square planar. In a rough approximation, the metal preferred bite angle for *cis*-coordinated bidentate ligands is 90° in a square planar [81]. Ligands with smaller bite angle such as dppp and binap produced less sterically hindered palladium center, therefore, the hydrogen is added to the terminal carbon of the triple bond and palladium center is coordinated to the internal carbon atom, the intermediate obtained is a pro-branched isomer complex with finally yield *gem*-isomer **(2.1).**

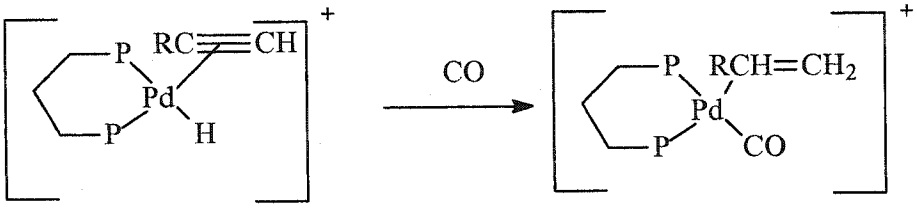
Ligands with larger bite angle such as dppb produced a more sterically crowded palladium center. As the result, palladium complex is attached to the terminal carbon and hydrogen to the internal carbon of the triple bond, leading to the production of pro-linear intermediate and finally, *trans*-$\alpha,\beta$-unsaturated amide **(2.2)** (Figure 2.2).



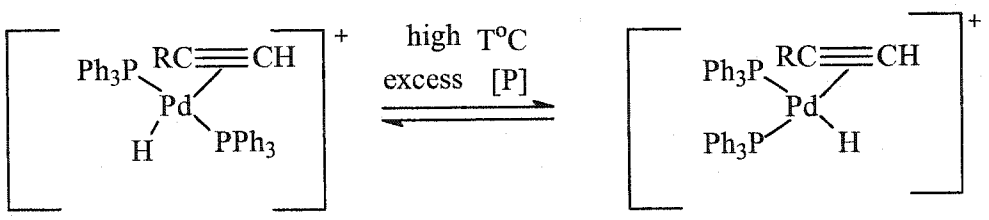

PRO-BRANCHED PRO-LINEAR

**Figure 2.2** Effect of ligand bite angle on regioselectivity

The most obvious difference between monodentate and bidentate ligands is that the later are always *cis*-coordinated (relation between the fourth coordinated and the reaction center), whereas the former coordinate in *trans* fashion [88]. If bidentate ligands are used the empty fourth coordinated site (or the hydride or CO site) is always *cis* to the $\pi$-coordinated alkyne site, and this is the most favorable position for hydride insertion reaction. When monodentate ligands are used, the fourth-coordinated site preferred *trans* orientation trans to $\pi$-alkyne site, *cis-trans* isomerization (to favorable *cis*-position) is likely to take place at high temperature or when excess amount of ligand are used [10,88] (Scheme 5).




*Cis*-ralation between the coordinated organic molecule and the carbonyl group (or hydride)

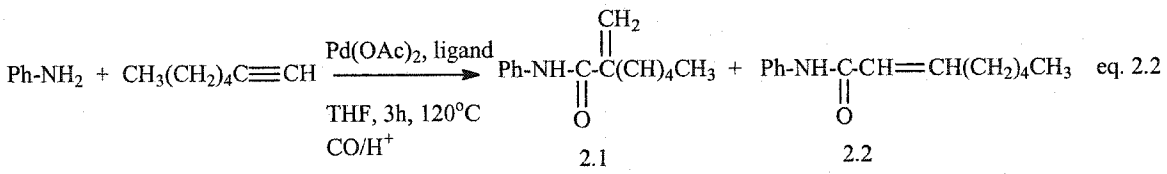



*Cis-trans* isomerization

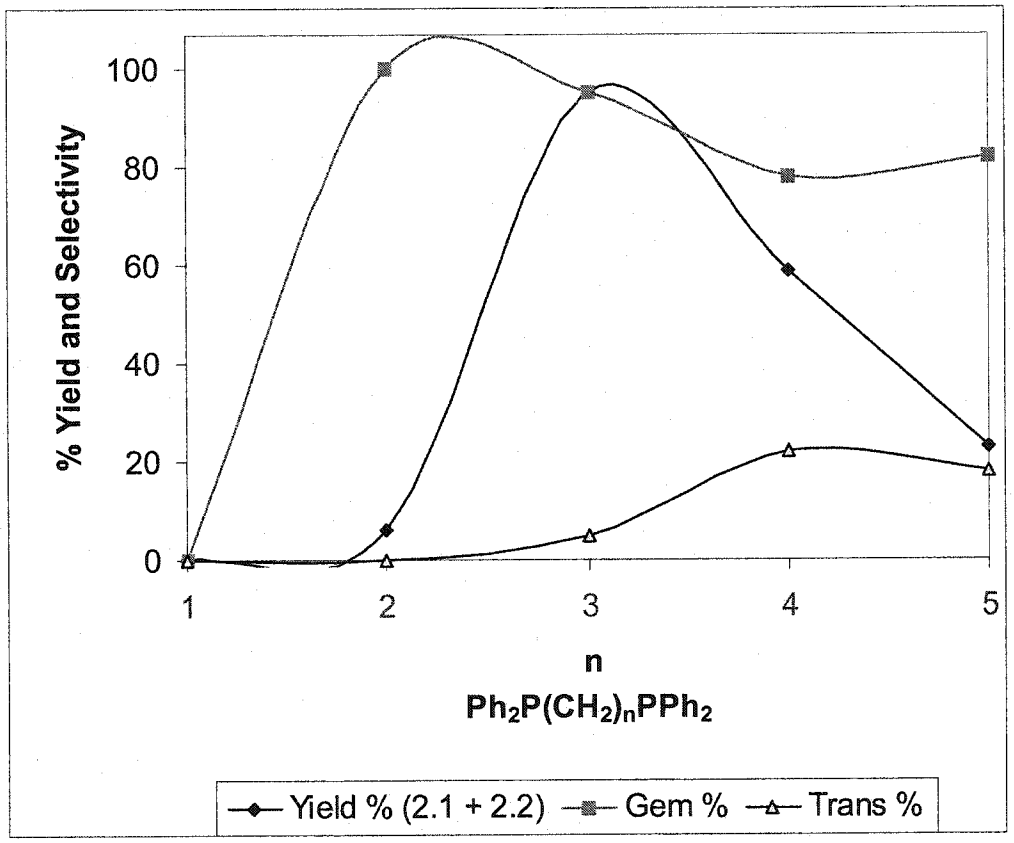
Scheme 5

A similar correlation between diphosphine ligand bite angle, catalytic efficiency and selectivity were observed in Pd-catalyzed cross coupling reactions of Grignard reagents with organic halides. Hayashi *et al.* [89] found that the increase in reaction rate occurred with increase of ligand bite angles, the slowest was observed with dppe (85°) and dppf (96°) was found to be the most reactive. The selectivity of the decreases again if ligands with bite angles above 102° is employed. Other examples include Pt-diphosphine-tin catalyzed hydroformylation [90], rhodium catalyzed hydroformylation [91], and Diels-Alder reactions [92]. Some catalytic reactions for example, nickel-diphosphine catalyzed hydrocyanation, are successful only if ligands with very large bite angles (>100°) are employed [93]

**Carbonylative coupling of 1-heptyne with aniline catalyzed by $Pd(OAc)_2$/ligand/$CO/H^+$; Effect of different bidentate ligands (chain length)**



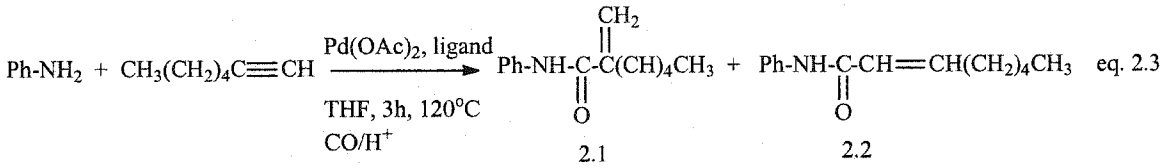

Ligands = dppm, dppe, dppp, dppb, dpppt



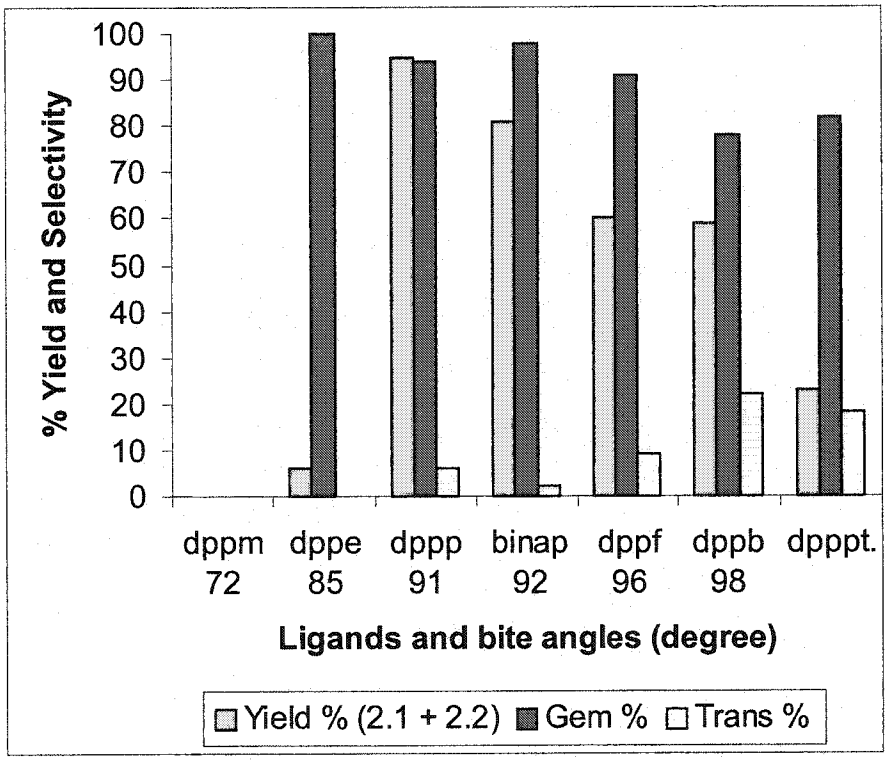

General reaction conditions: $Pd(OAc)_2$ (0.02 mmol), ligand (0.04 mmol), aniline & 1-heptyne (2.0 mmol), THF (10.0 ml), *p*-TsOH (0.12 mmol), CO (100 psi), 120°C, 3h.

**Figure 2.3**

**Carbonylative coupling of 1-heptyne with aniline catalyzed by $Pd(OAc)_2$/ligand/$CO/H^+$; Effect of different bidentate ligands (bite angle)**




Ligands = dppm, dppe, dppp, binap, dppf, dppb, dpppt




General reaction conditions: $Pd(OAc)_2$ (0.02 mmol), ligand (0.04 mmol), aniline & 1-heptyne (2.0 mmol), THF(10.0 ml), *p*-TsOH (0.12 mmol), CO (100 psi), 120°C, 3h.

**Figure 2.4**

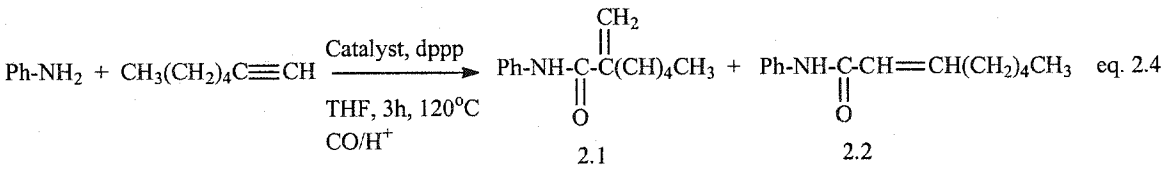
### 2.2.2. Catalytic activities of various metals complexes

The activity of different catalyst precursors in the carbonylation of 1-heptyne with aniline is shown in Table 2.1. $Ru_3(CO)_{12}$, $RhH(CO)(PPh_3)_3$, $Ni(OAc)_2.4H_2O$, and $Co(OAc)_2.4H_2O$ have no catalytic activity even in the presence of dppp ligand. While $NiCl_2$(dppp), $PdCl_2(PhCN)_2$, $PdCl_2$, $PdCl_2(PPh_3)_2$ gave isolated total yield of 6, 12, 13, and 23% respectively (Table 2.1, entries 1.1, 1.2, 1.3 and1.4). The low catalytic activity of the later complexes could be explained by the presence of chloride ions known to inhibit the activity of Pd catalysts [94]. Alper [76] confirmed these results in the hydrocarboxylation of terminal alkynes; the addition of NaOAc to $PdCl_2/PPh_3$/dppp system increased the yield of the products from 15 to 77%, due to the precipitation of chloride ions as insoluble NaCl.

The reason for the inhibition was the strong coordination of chloride ion to the palladium center to form the so-called neutral complexes [95] or the decomposition of active catalytic species [96] by the chloride ion. The use of $PdCl_2(PhCN)_2$ (Table 1, entry 1.4) shows an increase in the amount of *trans*-isomer **2.2**, which is probably related to the strong coordination ability of benzonitrile, which increase steric bulkiness around the palladium center and hence increase the tendency to form *trans* isomer.

$PtCl_2$(COD) gave about 50% yield of products (**2.1** and **2.2**) at 120°C (Table 2.1, entry; the results are better than those obtained Pt/Sn catalytic system [49] that gave 40% polymer as by-products at 100°C. Pd(0) such as $Pd(dba)_2$ and $Pd(PPh_3)_4$ has lower activity than $Pd(OAc)_2$ because they have to be converted to palladium cationic (by reacting with *p*-TsOH), which is presumably the precursor for the active catalytic specie [97] (eq. 2.3). The low catalytic activity of Pd/C 10% (Table 1, entries 1.1, 1.5 and 1.6)

**TABLE 1. Carbonylative coupling of 1-heptyne with aniline catalyzed by catalyst/dppp/CO/$H^+$; Effect of other metal catalysts**




| Entry | Catalyst | Yield %[a] | Selectivity %[b] 2.1: 2.2 |
|---|---|---|---|
| 1.1 | Pd/C 10% | 0 | 0:0 |
| 1.2 | $PdCl_2$ | 13 | 100:0 |
| 1.3 | $PdCl_2(PPh_3)_2$ | 23 | 100:0 |
| 1.4 | $PdCl_2(PhCN)_2$ | 12 | 48:52 |
| 1.5 | $Pd(dba)_2$ | 89 | 94:6 |
| 1.6[c] | $Pd(PPh_3)_4$ | 50 | 95:5 |
| 1.7[c] | $Pd(OAc)_2$ | 94 | 94:6 |
| 1.8[c] | $Pd(OAc)_2$(dppp) | 95 | 94:6 |
| 1.9[c,d] | $Pd(OTs)_2$(dppp) | 40 | 93:7 |
| 1.10 | $NiCl_2$(dppp) | 6 | 100:0 |
| 1.11 | $PtCl_2$(COD) | 50 | 97:3 |

General reaction conditions: catalyst (0.02 mmol), dppp (0.04 mmol), aniline &1-heptyne (2.0 mmol), THF (10.0 mmol), *p*-TsOH (0.12 mmol), CO (100 psi), thf (10 ml), 120°C, 6h (a) Isolated total yield (2.1+ 2.2) (b) Determined by GC and $^1H$ NMR (c) 3h (d) Additional acid *p*-TsOH was not used.

is also an indication of cationic palladium complex as the active catalytic specie.

$$L_nPd(0) + \text{p-TsOH} \rightleftharpoons [L_nPd{-}H] + TsO^- \qquad \text{eq. 2.5}$$

n, m = 3 or 4

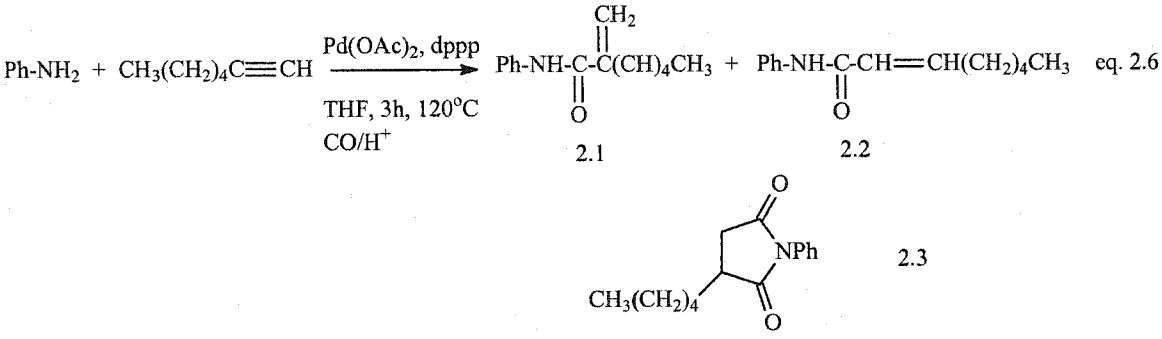
$Pd(OTs)_2(dppp)$ was synthesized and used without addition of an extra *p*-TsOH acid, the yield dropped to 40% (Table 1, entry 1.9). The results explained that excess of *p*-TsOH acid is needed to keep the catalyst in the active cationic form [97], and also proved that $OTs^-$ is probably not directly coordinated to Pd center but acts as counter ion [98].

### 2.2.3 Effect of substrate/palladium ratio

The effect of substrate to palladium acetate ratio on the carbonylation of 1-heptyne with aniline is shown on Figure 2.5. No reaction was observed in the absence of palladium catalyst. Generally, the increasing substrate to catalyst ratio decreases the yield and slightly affects the selectivity of *gem*-$\alpha,\beta$-unsaturated amide **(2.1)**. The highest selectivity (95%) with lowest isolated yield (38%) was obtained with substrate to catalyst ratio of 400. As the ratio is decreased to 200 the selectivity toward **2.1** was 94 %, and the yield increased form 38% to 61%. However, ratio of 100 gave 95% yield and 93% selectivity of **2.1**, hence is the optimum ratio with respect to yield and selectivity toward *gem*-$\alpha,\beta$-unsaturated amides.

A gradual decrease in selectivity of *gem* product was observed with increase in the amount of catalyst (decrease in substrate to [Pd] ratio) due to the increase in the formation of the cyclic substituted imide **(2.3)** ( *N*-phenyl-α-pentyl succinimide).

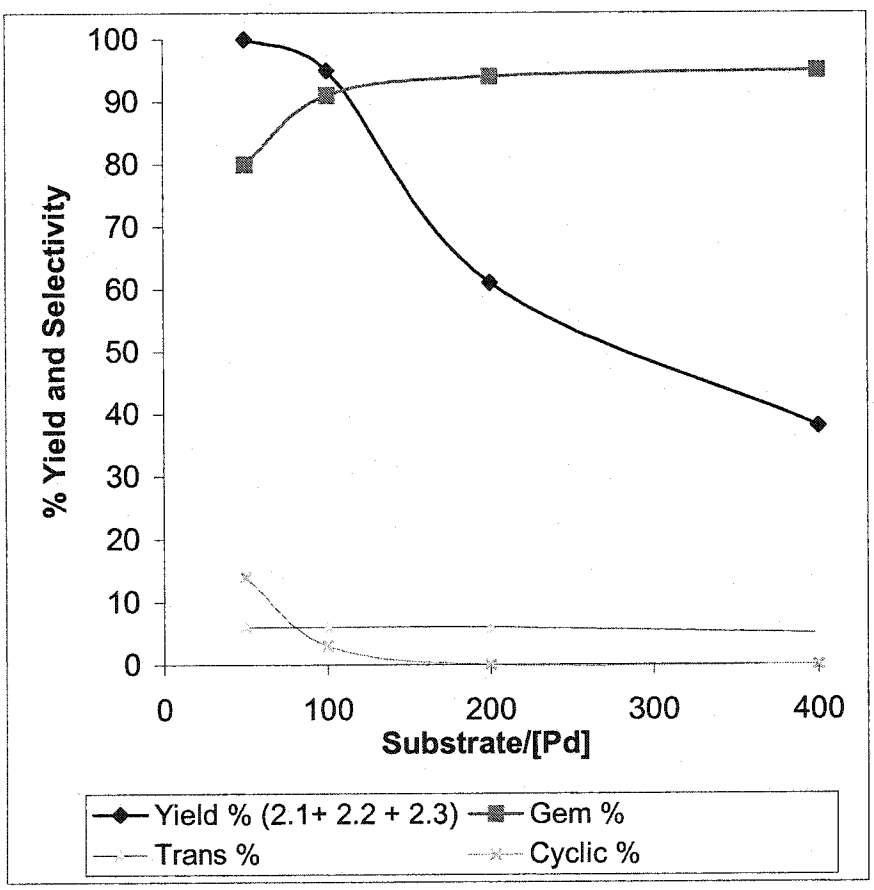
**Carbonylative coupling of 1-heptyne with aniline catalyzed by $Pd(OAc)_2$/dppp/$CO/H^+$; Effect of substrate to [Pd] ratio**







2.3




General reaction conditions: $Pd(OAc)_2$ (0.0-0.04 mmol), dppp (0.04 mmol), aniline & 1-heptyne (2.0 mmol), THF (10.0 ml), *p*-TsOH (0.12 mmol), CO (100 psi), 120°C, 3h.

**Figure 2.5**

### 2.2.4 Effect of ligand to catalyst ratio

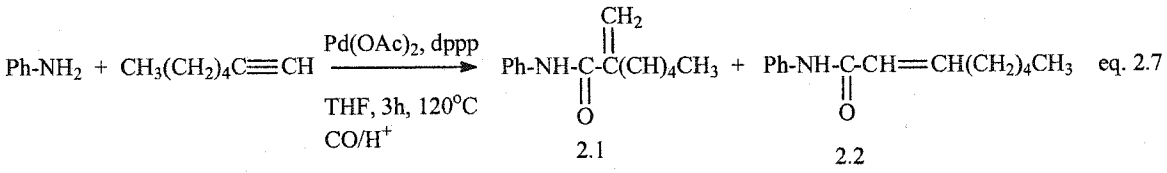
The effect of varying the ratio of ligand to catalyst on the catalytic carbonylative coupling of 1-heptyne with aniline is shown on Figure 2.6. Only traces of products were detected in the absence of ligand. The increase in the ligand to catalyst ratio generally increases the yield, and slightly decreases the selectivity. At the ligand to catalyst ratio of 0.5 the total yield of product was 47% and selectivity for *gem*-$\alpha,\beta$-unsaturated amide **(2.1)** was 95%; the low yield was connected to the lack of sufficient amount of ligand to stabilize the catalyst, hence it is precipitated as inactive palladium black. No such precipitation was observed with a molar ratio dppp/[Pd] higher than 2. The optimal ratio was 2 (95% yield and 93% selectivity for **2.1**). Further increases in the ratio to 4 resulted in the decrease of the yield, because ligand competes with the reactant molecules for coordination site.

The selectivity of the reaction remains fairly constant for various ratios i.e. it is independent of the amount of the ligand but mainly depends on the nature of the ligand, precisely on its bite angle (Section 2.2.1). Four phosphines to every palladium were also found to be the optimum in palladium-mediated carbonylation and coupling of iodobenzene with aniline [99] and palladium catalyst regioselective hydrocarboxylation of 4-methylstyrene [100].

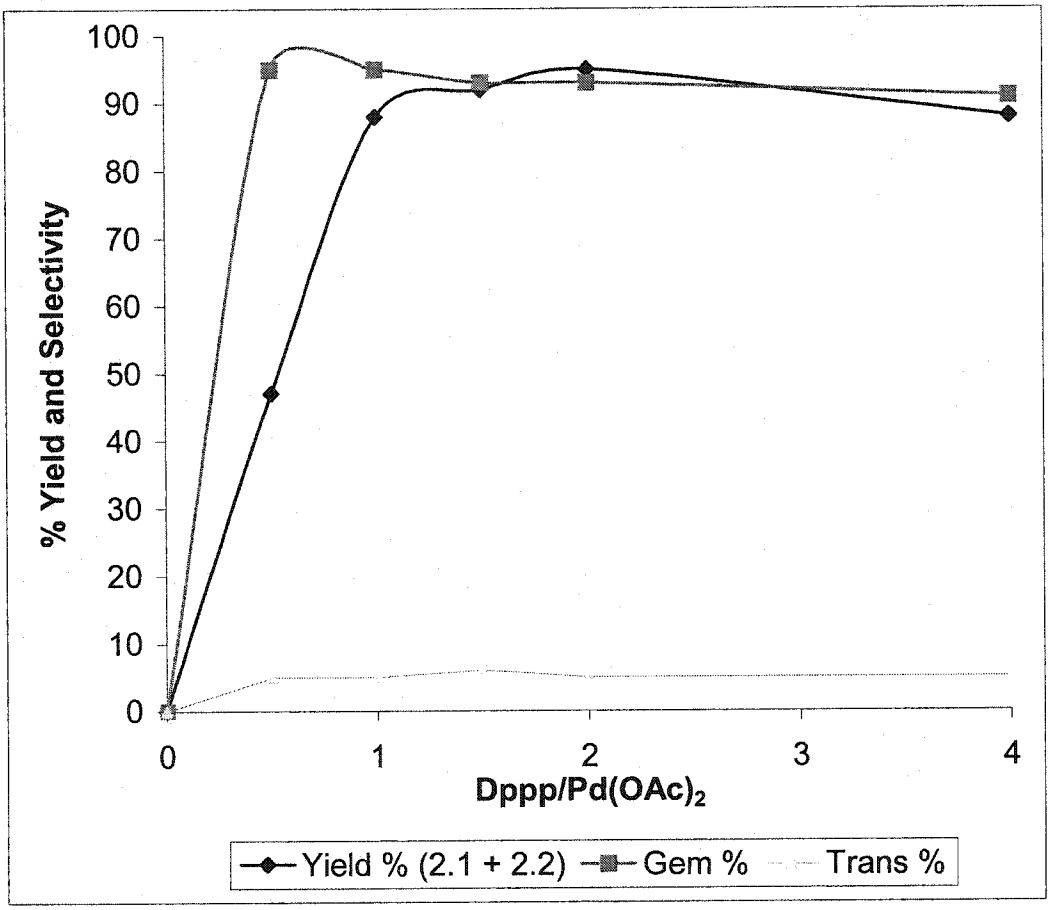
### 2.2.5 Effect of the reaction time

The effect of varying the reaction time on the yield and selectivity in the catalytic carbonylative coupling of 1-heptyne with aniline in THF and toluene was studied (Figure

**Carbonylative coupling of 1-heptyne with aniline catalyzed by $Pd(OAc)_2$/dppp/$CO/H^+$; Effect of the ligand to catalyst ratio**



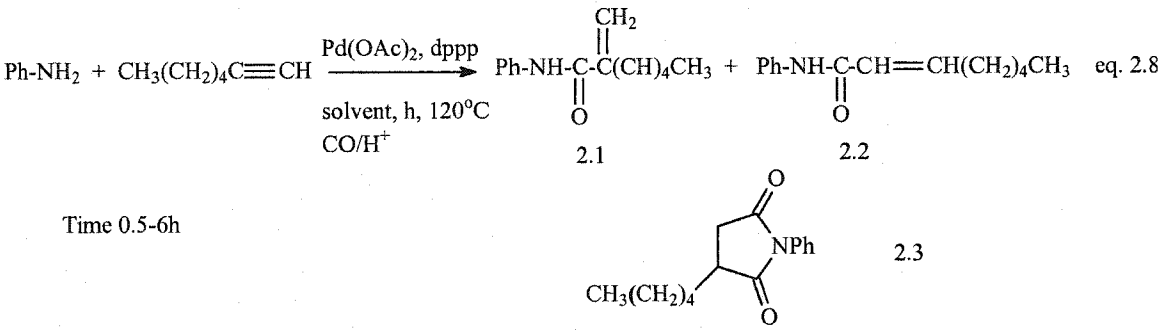
eq. 2.7

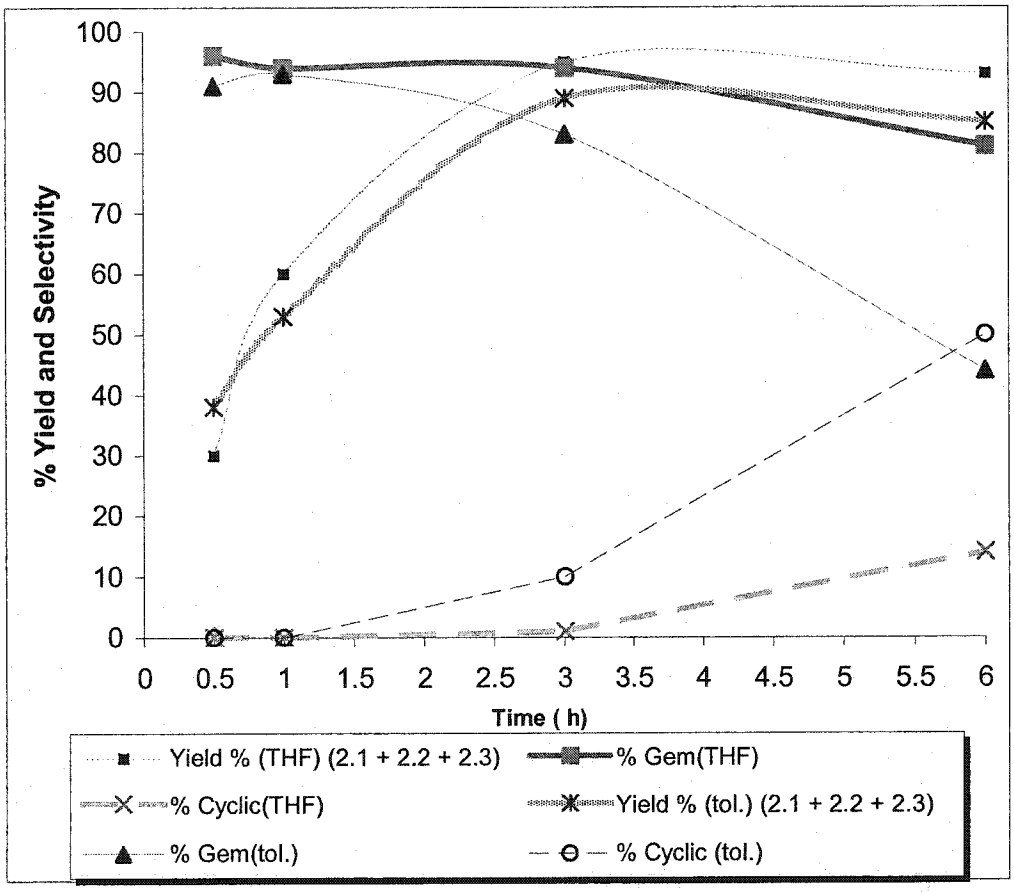



General reaction conditions: $Pd(OAc)_2$ (0.02 mmol), dppp (0.0-0.08 mmol), aniline &1-heptyne (2.0 mmol), THF (10.0 ml), *p*-TsOH (0.12 mmol), CO (100 psi), 120°C, 3h.

**Figure 2.6**

**Carbonylative coupling of 1-heptyne with aniline catalyzed by $Pd(OAc)_2$/dppp/CO/$H^+$; Effect of reaction time**




General reaction conditions: $Pd(OAc)_2$ (0.02 mmol), dppp (0.04 mmol), aniline & 1-heptyne (2.0 mmol), toluene & THF (10.0 ml), *p*-TsOH (0.12 mmol), CO (100 psi), 120°C, 0.5-6h.

**Figure 2.7**

2.7). Generally, the yield increases with time but the selectivity toward *gem*-isomer decreases **(2.1)**. The optimum reaction time was three hours for both solvents.

The formation of the cyclic compound **(2.3)** is also increased with the reaction time, little or no cyclic product was observed for an hour reaction. The amount of *trans*-$\alpha,\beta$-unsaturated amide **(2.2)** produced remains fairly constant throughout the reaction.

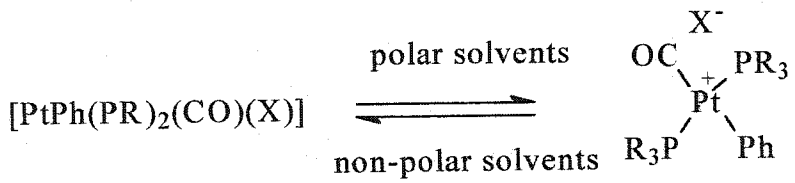
The yield and the selectivity of *gem* product are higher in THF compared to toluene as solvent. The rate of the reaction is faster with THF, i.e. 60% yield after an hour compared to 33% in toluene. The selectivity for **(2.1)** was maintained higher in THF (81% after 6h) than toluene (48% after 6h), due to the formation of substituted cyclic imide **(2.3)**.

### 2.2.6 Effect of solvents

The results of the effect of different solvents on the carbonylative coupling of 1-heptyne with aniline are shown in Table 2. The results show no correlation between the dielectric constant of the solvent and the yield and selectivity of the reaction. The catalytic activity was strongly influenced by the polarity of the solvent. Non-polar solvents such as toluene, and dimethyl ether gave good catalytic activity. Slightly polar solvent such as tetrahydrofuran gave the best results. The more polar solvent such as acetonitrile and ethyl acetate gave conversion and the catalyst was found deactivated to palladium metal after the reaction [98].

In slightly polar solvents the complex and the counter ion have higher ionic character than in non-polar solvent; the solvation of the ion-pairs by fairly polar solvent molecules is expected to facilitate cation-anion dissociation and therefore render the metal

center more electrophilic and more accessible for the substrate molecules. In relatively apolar solvents close-contact ion-pairs are generally expected to exist [10]. High degree of covalency is also high in apolar solvents this make the rate of reaction is slower [101] (eq. 2.9).



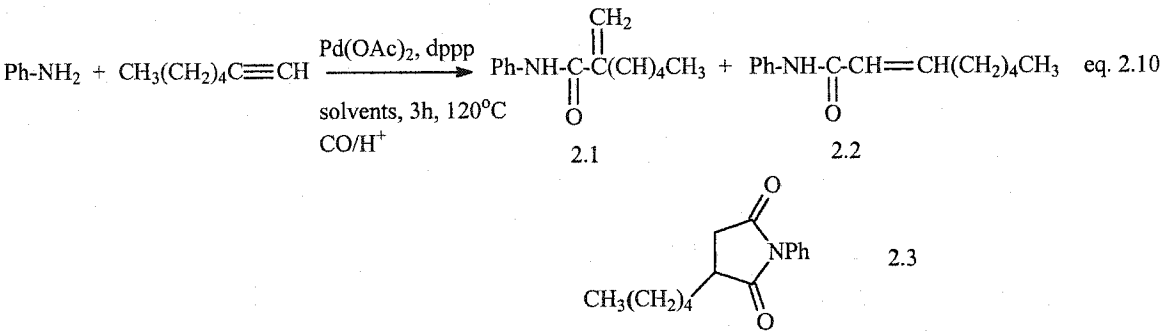

eq. 2.9

R = alkyl or aryl and x = halide

Acetonitrile seems to be particularly poor solvent perhaps, because of its tendency to bond strongly to palladium center, and probably replaces the active ligand and substrate in the coordination site [35]. The reversal in the selectivity toward *trans* product is probably due to the same reason (Table 2, entry 2.7). Dichloromethane and toluene are the best solvents for synthesis of *trans* and cyclic respectively (Table 2, entries 2.5 and 2.9). Why more cyclic product **(2.3)** was formed in toluene than in THF? Is the intermediate for the formation of **2.3** more stable in toluene? The reason is still not clear, but a previous report shows that the cyclization of benzaldehyde to phthalimidine occurred only in non-polar aromatic or aliphatic hydrocarbon (e.g. toluene), no such cyclic compound is formed in THF [102] or in any other polar solvent.

Furthermore, lower yield (47%) was obtained by doubling the amount of solvent i.e. by reducing the concentration of the substrate while the selectivity remains unchanged (Table 2, entry 2.4). Whereas increasing the concentration of the reactants maintain the

**TABLE 2: Carbonylative coupling of 1-heptyne with aniline catalyzed by Pd(OAc)2/dppp/CO/$H^+$; Effect of different solvents**




| Entry | Solvent | Volume (ml) | Yield [a] % | Selectivity [b]% 2.1: 2.2: 2.3 |
|---|---|---|---|---|
| 2.1 | THF | 5 | 95 | 87:9:4 |
| 2.2 | THF | 10 | 94 | 94:4:2 |
| 2.3 | THF | 15 | 77 | 94:6:0 |
| 2.4 | THF | 20 | 47 | 95:5:0 |
| 2.5 | Toluene | 10 | 89 | 83:7:10 |
| 2.6 | DME | 10 | 88 | 87:4:9 |
| 2.7 | $CH_3CN$ | 10 | 15 | 27:73:0 |
| 2.8 | Ethyl acetate | 10 | 12 | 95:5:0 |
| 2.9 | $CH_2Cl_2$ | 10 | 31 | 87:13:0 |

General reaction conditions: $Pd(OAc)_2$ (0.02 mmol), dppp (0.04 mmol), aniline & 1-heptyne (2.0 mmol), solvent (10.0 ml), *p*-TsOH (0.12 mmol), CO (100 psi), 120°C, 3h (a) Isolated total yield 2.1 + 2.2 + 2.3 (b) Determined by GC and $^1H$ NMR

yield (95%) and slightly lower the selectivity for the *gem*-$\alpha,\beta$-unsaturated amide (87%) by increasing the amount of *trans*--$\alpha,\beta$-unsaturated amide and cyclic (Table 2, entry 2.1).

### 2.2.7 Effect of acidity

Table 3 and Figure 2.7 show the effect of the type and the amount of acid on the catalytic carbonylation of 1-heptyne with aniline. The activity of various acids decreases in the order: *p*-TsOH > $CF_3CO_2H$ > $CH_3SO_3H$ acid > Pyridine-2,5-dicarboxylic acid > *p*-nitrobenzoic acid > HCl, which is the inverse of the coordination ability of the corresponding anion, this result is similar to what was observed previously in the hydroesterification of styrene [97]. Higher activity was obtained with sulphonic acids due probable to the presence of traces of water, which enhances the formation of $L_nPd$-H through water gas shift reaction [97,98] (Scheme 6).

$$[L_nPd]^+ + CO + H_2O \xrightarrow[-H^+]{} [L_nPd(CO_2H]^+ \longrightarrow [L_nPd\text{-}H]^+ + CO_2$$

n = 3 or 4

Scheme 6

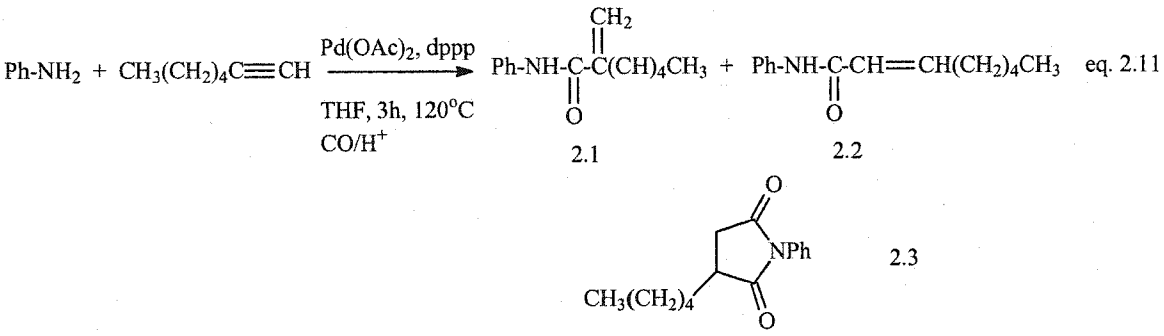
The presence of ion having higher binding abilities (Table 3, entry 3.6) reduces the availability of the coordination sites around the central metal atom leading to lower catalytic activity [97,98]. Oxalic acid and acetic acid [103,104,] used as promoter in hydrocarboxylation reaction are found to be inactive under our reaction conditions. It is suggested that, in general, the coordination strength of anions toward the cationic palladium center depends to a certain extent on acid strength of the corresponding Bronsted acids. Exception to the rule comprises halide anions, which are although derived from strong acids, strongly coordinate to Pd(II). Therefore, it is concluded that

coordination rather than acid/base properties determine the effect of anions on catalytic performance [95]. The higher reactivity with weakly coordinating anions is thought to arise, in part, from the easier access of substrate molecules as well as phosphine ligand to the coordination sites around the metal center [95]..

The basic question is concerning the role of the acid in the carbonylation reaction. The acid may react by forming metal hydride species, by protonating the electron-rich metal center. Pd(0) species (formed from *in situ* reduction of Pd(II) when heated in the presence of CO [96]) are electron-rich and are known to form Pd-H in the presence of strong acid. The $OTs^-$ anion can either coordinate to the metal to give neutral compound, or act as a counter-anion to the cationic species. The later is more plausible in the present system for three reasons: firstly, the coordination of the $OTs^-$ anion would render it prone to hydrogenation of the alkynes to alkenes and alkanes [35], the second reason is the displacement of weakly coordinating labile anions from the sphere of metals by less labile ligands, this is well documented in the literature [105]. And finally, weakly coordinating anions, because of their easier dissociation from ion-pair, generate a more electrophilic palladium center [10,88].

The selectivity is not affected much by the change in the concentration of *p*-TsOH, which suggested that $OTs^-$ might not be strongly coordinated to the Pd center [97], but act as counter anion. Most of the other acids required longer reaction time to give the same yield, for example, benzoic acid gave after 24 hours over 90% yield with almost the same selectivity (Table 3, entry 3.8).

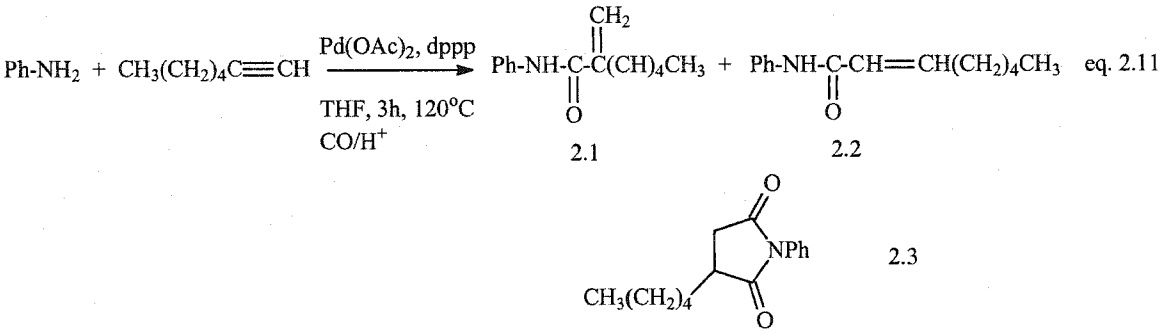
**TABLE 3. Carbonylative coupling of 1-heptyne with aniline catalyzed by $Pd(OAc)_2$/dppp/$CO/H^+$; Effect of different types of acid.**




| Entry | Acid | Yield %[a] | Selectivity %[b] 2.1:2.2:2.3 |
|---|---|---|---|
| 3.1 | *p*-TsOH | 95 | 92:5:3 |
| 3.2 | $CF_3CO_2H$ | 80 | 93:5:2 |
| 3.3 | $CH_3SO_3H$ | 70 | 91:4:5 |
| 3.4[c] | Pyda[d] | 11 | 100:0:0 |
| 3.5 | *p*-Nitrobenzoic acid | 3 | 100:0:0 |
| 3.6 | HCl | 1 | 100:0:0 |
| 3.7 | Benzoic acid | Traces | Traces |
| 3.8[e] | Benzoic acid | 91 | 91:6:3 |
| 3.9 | $CH_3CO_2H$ | Traces | Traces |

General reaction conditions: $Pd(OAc)_2$ (0.02 mmol), dppp (0.04 mmol), aniline& 1-heptye (2.0 mmol), THF (10.0 mmol), acid (0.12 mmol), CO (100 psi), 120°C, time 3h (a) Isolated yield 2.1+ 2.2 + 2.3 (b) Determined by GC and $^1H$ NMR (c) Pyridine-2,5-dicarboxylic acid (d) 0.06 mmol (e) 24h.

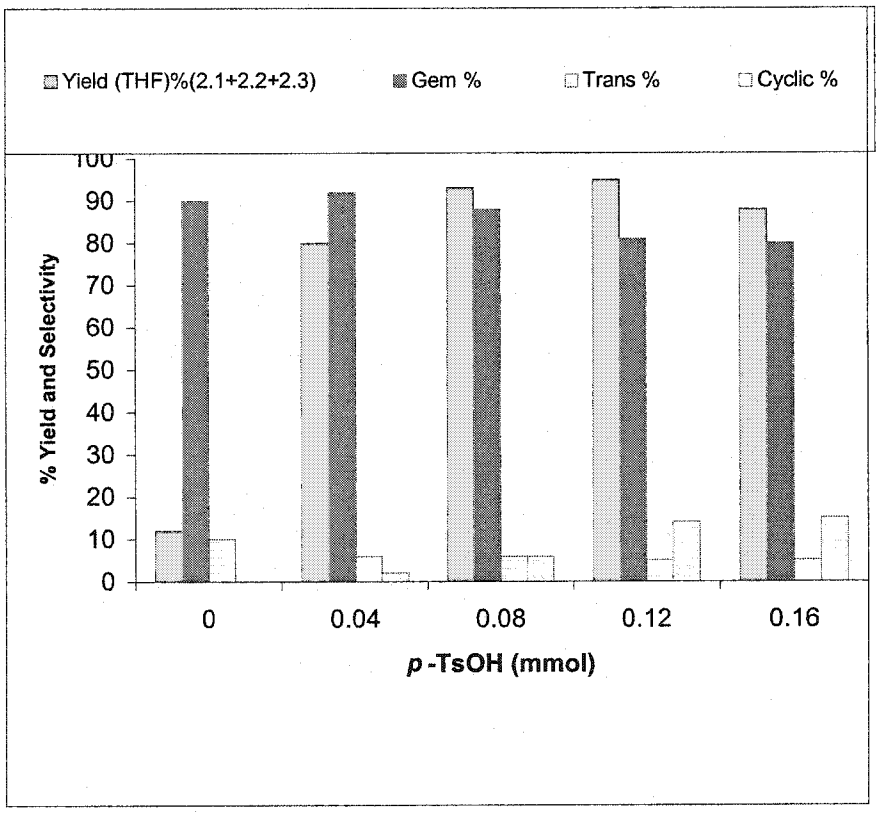
**Carbonylative coupling of 1-heptyne with aniline catalyzed by $Pd(OAc)_2$/dppp/$CO/H^+$; Effect of amount of acids**







2.3

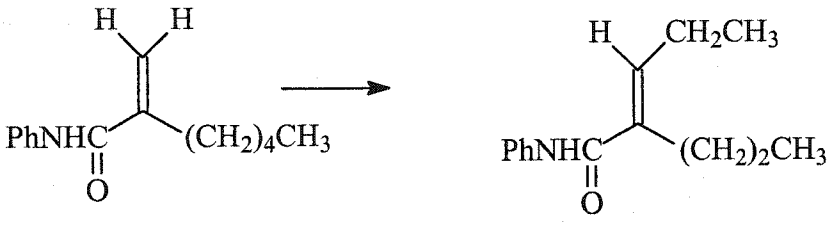



General reaction conditions: $Pd(OAc)_2$ (0.02 mmol), dppp (0.04 mmol), aniline & 1-heptyne (2.0 mmol), THF(10.0 ml), *p*-TsOH (0.0-0.16 mmol), CO (100 psi), 120°C, 3h.

**Figure 2.8**

### 2.2.8 Effect of temperature

The effect of the temperature on the catalytic carbonylation of 1-heptyne with aniline has been studied (Figure 2.9). The optimum temperature is 120°C; lower temperatures resulted in lower conversions and yield, with the selectivity remains almost the same. At higher temperature the yield for *gem* **(2.1)** decreased, due to its isomerization to *N*-phenyl-2-propyl penteneamide **(2.4)** (~9% was formed) (eq. 2.12). This type of isomerization is very similar to sigmatrophic migration involving alkyl (1,3-ethyl shift) [106].




2.1 2.4

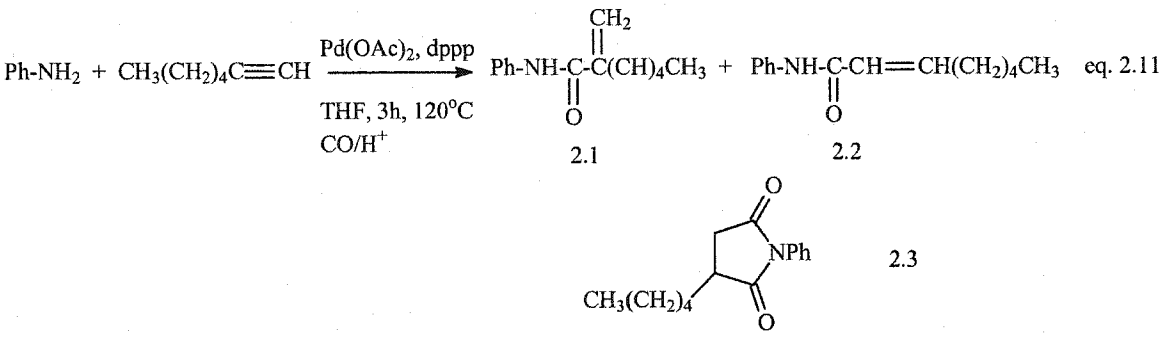
eq. 2.12

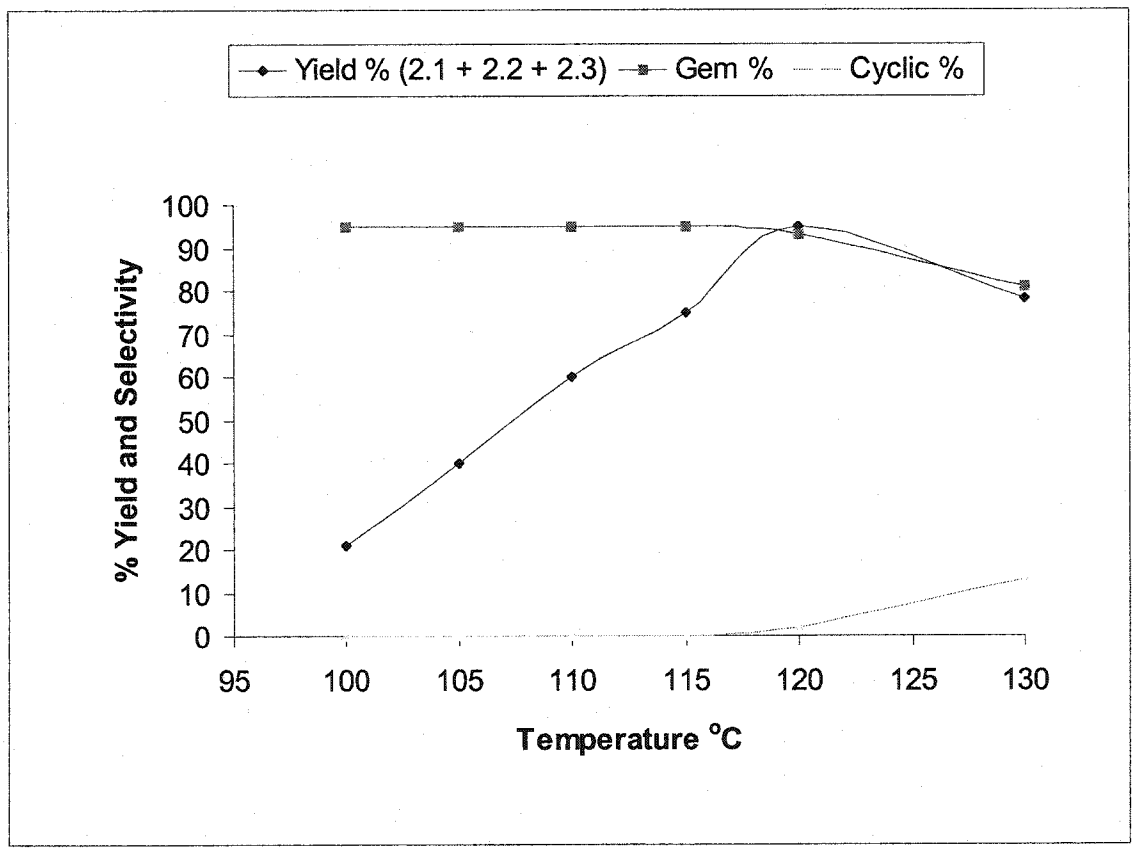
Is the cyclic product **(2.3)** coming from **2.1** or / and **2.2**? Or was **2.3** formed through an independent route? If we compare its selectivity in toluene at 120°C and 6h (ratio of *gem:trans:cyclic* equals to 48:5:47) with the same solvent at the same temperature but after 3h of reaction time the ratio change to 83:7:10 (Table 2, entry 2.5). Therefore, we suggest that most of the **2.3** might come from **2.1**. Synthesis of cyclic has been reported from unsaturated amide using cobalt catalyst at elevated temperature [14].

### 2.2.9 Effect of CO pressure

The data on Figure 2.10 shows that the presence of CO gas is essential for the catalytic carbonylative coupling of alkynes with aniline derivatives. Virtually no product

**Carbonylative coupling of 1-heptyne with aniline catalyzed by $Pd(OAc)_2$/dppp/$CO/H^+$; Effect of temperature**

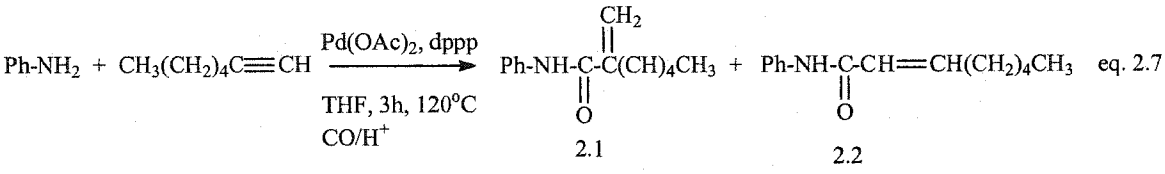


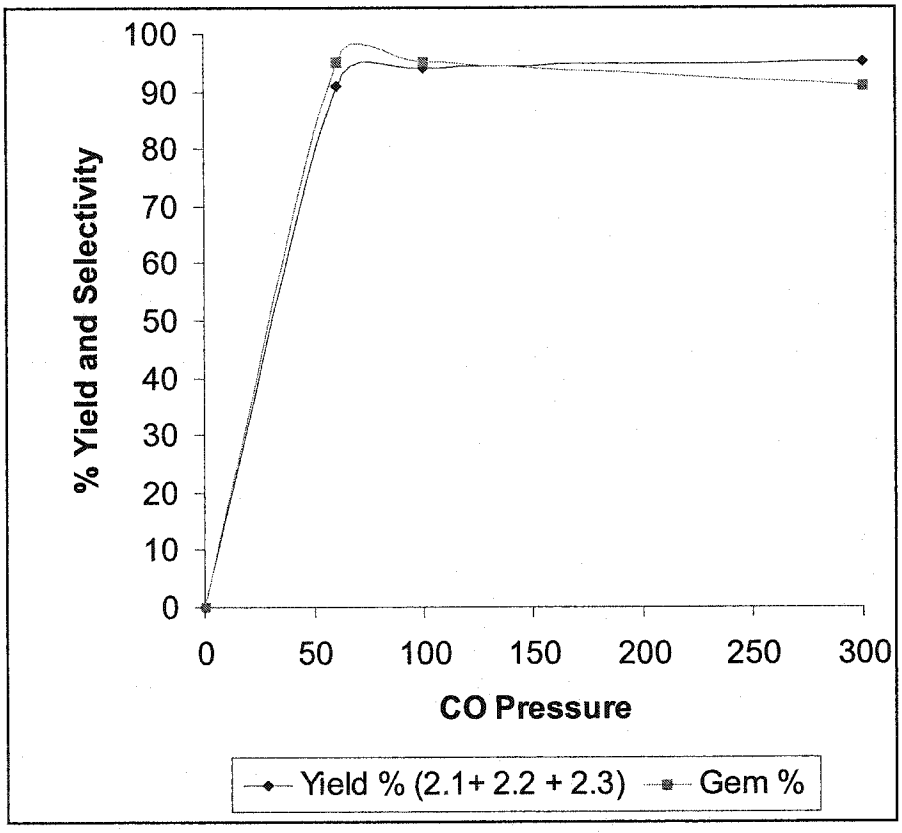




General reaction conditions: $Pd(OAc)_2$ (0.02 mmol), dppp (0.04 mmol), aniline & 1-heptyne (2.0 mmol), THF (10.0 ml), *p*-TsOH (0.12 mmol), CO (100 psi), 100-130°C, 3h.

**Figure 2.9**

**Carbonylative coupling of 1-heptyne with aniline catalyzed by $Pd(OAc)_2$/dppp/$CO/H^+$; Effect of CO pressure**




General reaction condition: $Pd(OAc)_2$ (0.02 mmol), dppp (0.04 mmol), aniline & 1-heptyne (2.0 mmol), THF (10.0 ml), *p*-TsOH (0.12 mmol), CO (0-300 psi), 120°C, 3h.

**Figure 2.10**

was formed in the absence of CO. Up to 95% of products was obtained at pressure of 100 psi, further increased in the pressure doesn't offer any advantage. Since the solubility of CO gas in solvents is proportional to (among other factors) the CO pressure; these results imply that, 100 psi is sufficient to dissolve enough CO in the reaction medium, a vital step in the carbonylation [76]. The amount of *trans* products **(2.2)** remained fairly constant (~5 %), with about 3 % cyclic product **(2.3)** at 300 psi.

### 2.2.10 Catalytic Carbonylation of different terminal alkynes with aniline derivatives

The carbonylation of different aniline derivatives with various terminal alkynes has been realized (Table 4). The reaction of *p*-chloroaniline and aniline with 1-heptyne were almost completed in three hours, whereas the complete conversion of *p*-chloroaniline and aniline with 1-pentyne and 1-nonye required at least 6h. 5-Hexynenitrile gave *gem* isomers regioselectively with 2,4-dimethylaniline and *N*-methyl aniline. The carbonylative coupling of 1-pentyne with aniline and *p*-chloroaniline yield 74 and 86% of *gem* isomers, 15 and 10 % cyclic products, respectively. All the reactions involving 3,3-dimethyl-1-butyne were slower and required longer reaction time (at least 15h) for completion.

The carbonylative coupling of 3,3-dimethyl-1-butyne with aniline gave 90% *gem*--*α,β*-unsaturated amide **(α-4.5)** *N*-pheyl-2-(3,3-methylethyl) propeneamide and 10% trans-α,β-unsaturated **(β-9.5)** *N*-phenyl-4,4-dimethyl-2-buteneamide. The *regio-* and *stereochemistry* of the two isomers can easily be distinguish by the $^{1}$H NMR, $^{13}$C NMR and FT-IR. The signal for the two-*geminal* protons in **α-4.5** became very close and appear as doublet at 5.33-5.38 (J 25.05). Whereas **β-9.5** has two doublets at 5.81-5.84 (J

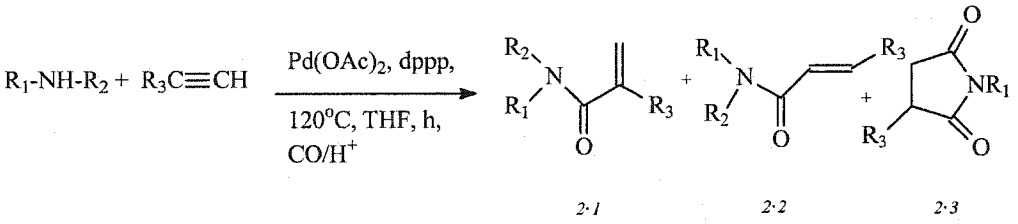
= 15.25) and 6.98-7.01 (J = 15.25). The carbonyl signal identified with $^{13}C$ NMR and FT-IR for **α-4.5** was 169.18 ppm and 1656 $cm^{-}$, whereas that of **β-9.5** was 164.54 ppm and 1668 $cm^{-}$ respectively (Section 5.4).

The reactivity of aniline derivatives decreases in the following order: *p*-chloroaniline > aniline > 2-aminophenol > 2,4-dimethylaniline > *N*-methylaniline. This order reflects the activity of the proton (proton attached to the amino group). The reactivity of aniline (acidity of aniline) was enhanced by the introduction of an electron-withdrawing group on the ring, especially, in the *para*-position to the amino group causing a decrease in electron density on the ring. This effect is transmitted to the amino group, making the nitrogen atom more deficient in electrons and subsequently more acidic [107]. The reverse was observed when an electron-donating group is attached to the ring. The induction time with 2,4-dimethylaniline and *N*-methyl aniline as substrates is much longer, while the reaction for *p*-chloroaniline was completed in less then three hours.

However, with of 2-aminophenol (Table 4, entries 4.21-4.25) the competition between the inductive effects of oxygen atom of the hydroxyl, which tend to withdraw electrons from the ring and the interaction of electron pair of the oxygen with the benzene ring, which tend to enhance the availability of electron around the ring. Unfortunately, it is difficult to determine which of these two factors has the greater influence. It seems that the overall effect is to enhance the electron density of the ring [107] and as the subsequent decrease of the reactivity compared to aniline (Table 4, entries 4.1-4.5).

The nature of the alkyl group attached to 1-alkyne (*β*-substituent) molecule affects both the reactivity and the selectivity of the products. The observed pattern with 3,3-

**TABLE 4. Carbonylative coupling of different alkyl alkynes with aniline derivatives catalyzed by $Pd(OAc)_2$/dppp/CO/$H^+$**




eq. 2.13

| Entry | Alkynes $R_3$- | Aniline derivatives | Time H | Yield %[a] | *Gem(2.1)*[b] % | Selectivity %[c] *2.1:2.2:2:3* |
|---|---|---|---|---|---|---|
| 4.1 | $CN(CH_2)_3$- | Aniline; $R_1$= Ph; $R_2$ = H | 6 | 91 | β-4.1 | 95:5:0 |
| 4.2 | $CH_3(CH_2)_2$- | | 6 | 87 | β-4.2 | 74:5:15 |
| 4.3 | $CH_3(CH_2)_4$- | | 3 | 94 | β-4.3 | 93:5:2 |
| 4.4 | $CH_3(CH_2)_6$- | | 6 | 94 | β-4.4 | 89:5:6 |
| 4.5 | $(CH_3)_3C$- | | 15 | 81 | β-4.5 | 90:10:0 |
| 4.6 | $CN(CH_2)_3$- | *p*-Chloroaniline; $R_1$= *p*-$ClC_6H_4$; $R_2$ = H | 3 | 93 | β-4.6 | 92:8:0 |
| 4.7 | $CH_3(CH_2)_2$- | | 6 | 97 | β-4.7 | 86:4:10 |
| 4.8 | $CH_3(CH_2)_4$- | | 3 | 93 | β-4.8 | 88:8:4 |
| 4.9 | $CH_3(CH_2)_6$- | | 6 | 83 | β-4.9 | 94:6:0 |
| 4.10 | $(CH_3)_3C$- | | 15 | 86 | β-4.9 | 86:14:0 |

| Entry Cont. | 1-alkynes $R_3$- | Aniline derivatives | Time h | Yield %[a] | *Gem(2.1)* %[b] | Selectivity %[c] *2.1:2.2:2.3* |
|---|---|---|---|---|---|---|
| 4.11 | $CN(CH_2)_3$- | 2,4-Dimethylaniline $R_1$= 2,4-$(CH_3)_2C_6H_3$; $R_2$ = H | 15 | 94 | β-4.11 | 100:0:0 |
| 4.12 | $CH_3(CH_2)_2$- | | 15 | 73 | β-4.12 | 96:4:0 |
| 4.13 | $CH_3(CH_2)_4$- | | 6 | 83 | β-4.13 | 95:5:0 |
| 4.14 | $CH_3(CH_2)_6$- | | 15 | 77 | β-4.14 | 92:8:0 |
| 4.15 | $(CH_3)_3C$- | | 24 | 67 | β-4.15 | 90:10:0 |
| 4.16 | $CN(CH_2)_3$- | *N*-Methylaniline $R_1$= Ph; $R_2$ = $CH_3$ | 15 | 94 | β-4.16 | 100:0:0 |
| 4.17 | $CH_3(CH_2)_2$- | | 15 | 90 | β-4.17 | 96:4:0 |
| 4.18 | $CH_3(CH_2)_4$- | | 6 | 74 | β-4.18 | 96:4:0 |
| 4.19 | $CH_3(CH_2)_6$- | | 15 | 80 | β-4.19 | 96:4:0 |
| 4.20 | $(CH_3)_3C$- | | 24 | 60 | β-4.20 | 83:17:0 |
| 4.21 | $CN(CH_2)_3$- | 2-Aminophenol $R_1$= *o*-OH-$C_6H_4$; $R_2$ = H | 15 | 94 | β-4.21 | 90:10:0 |
| 4.22 | $CH_3(CH_2)_2$- | | 15 | 97 | β-4.22 | 90:10:0 |
| 4.23 | $CH_3(CH_2)_4$- | | 15 | 93 | β-4.23 | 92:8:0 |
| 4.24 | $CH_3(CH_2)_6$- | | 15 | 90 | β-4.24 | 91:9:0 |
| 4.25 | $(CH_3)_3C$- | | 15 | 95 | β-4.25 | 95:5:0 |

General reaction conditions: $Pd(OAc)_2$ (0.02 mmol), dppp (0.04 mmol), aniline derivatives & 1-alkynes (2.0 mmol), THF (10.0 ml), *p*-TsOH (0.12 mmol), CO (100 psi), 120°C, 3-24h (a) Isolated total yield 2.1 + 2.2 + 2.3 (b) Selectivity of 2.1:2.2:2.3, determined by GC and $^1$H NMR .

dimethyl-1-butyne reflects the important steric effect of the alkyl substituent, the bulky $\beta$-substituent, in reducing the accessibility of the active center, hence, the rate of carbonylative coupling of *mono*-substituted alkyl alkynes decreased [104]. The hydropalladation of terminal alkynes can also be affected by the electronic nature of the catalyst and the substrates. In 5-hexynenitrile the terminal carbon of the triple bond ($\alpha$-carbon) is slightly more nucleophilic compared to the internal carbon ($\beta$-carbon) due to the presence of the cyano group, therefore the terminal carbon is more likely to be attack by the proton than the internal carbon as the result the palladium center will coordinate to the internal carbon and thus produces the *gem* isomer **(2.1)**. Similarly, the relative lower nucleophilicity of the terminal carbon ($\alpha$-carbon) compared to the internal carbon ($\beta$-carbon) in 3,3-dimethyl-1-butyne slightly reduces the selectivity toward the *gem* isomer. The selectivity toward *gem*-$\alpha,\beta$-unsaturated amides by the different alkyl alkynes (Table 4) decreases is in the following order: $CN(CH_2)_3C- > CH_3(CH_2)_2C- > CH_3(CH_2)_4C -> CH_3(CH_2)_6C- > (CH_3)_3C-$, which reflects the order of electrophilicity of $\beta$-carbon of the triple bond.

The selectivity in the carbonylation of terminal alkynes was attributed to electronic effect of carbon, therefore, how can we explain the formation of *gem* as the major product with 3,3-dimethy-1-butyne while $\beta$-carbon is less electrophilic than $\alpha$-carbon? This could only be explained if we assume that the addition is stepwise, starting with the addition of the proton to the internal carbon, followed by 1,2-hydride shift to more stable secondary carbocation and then the coordination of the Pd complex to the internal carbon, and subsequent formation of *gem* isomer.

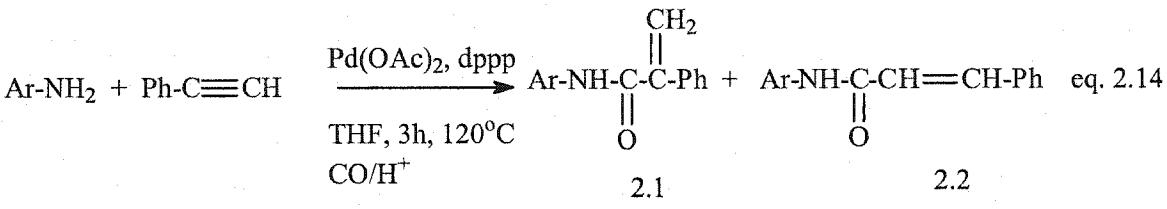
Generally, the velocity of the reaction is determined mostly by the electronic effect of the group attached to the ring or the amino group in aniline derivatives, whereas the selectivity is determined by the steric and electronic effect of the group attached to the alkyne, i.e. the regiochemistry is controlled by both steric and electronic factors, but the electronic factor seems to predominate in this system.

### 2.2.11 Catalytic Carbonylation of aryl acetylenes with aniline derivatives

The catalytic carbonylation of various aniline derivatives with phenylacetylene and *p*-methyl phenylacetylene has been studied (Table 5). The $\alpha,\beta$-unsaturated amides were isolated in total isolated yields (74-96%). The reaction exhibits high *regioselectivity* in favor of *gem* products. Phenylacetylene is more reactive and selective toward *gem* isomer than *p*-methyl phenylacetylene under the same reaction conditions this probably related to the reduction in electrophilicity of $\beta$-carbon by the inductive effect of the substituted methyl group on the benzene ring.

Other aniline derivatives have been considered with phenylacetylene (Table 5, entries, 5.3-5.8). High yields of the unsaturated amides and excellent selectivity of *gem* isomers were generally obtained. The low conversion of *N,N*-diphenylamine is obviously attributed to the steric effect caused by the presence of two phenyl groups. However, 1-naphthylamine, *N,N*-diphenyl aniline and *p*-chloroaniline react with phenylacetylene to form *gem* isomers as the sole products. The regiochemical outcome is in excellent accord with the related palladium-catalyzed hydrocarboxylation of terminal alkynes [35,76,101,102].

**TABLE 5. Carbonylation of terminal aromatic alkynes with aniline derivatives catalyzed by $Pd(OAc)_2$/dppp/$CO/H^+$.**



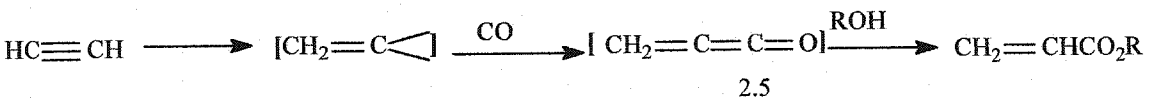

2.1 2.2

| Entry | Aniline Derivatives | Alkynes R- | *Gem* Prod. | Yield [a]% | Selectivity %[b] 2.1:2.2 |
|---|---|---|---|---|---|
| 5.1 | Aniline | Ph- | β-5.1 | 91 | 96:4 |
| 5.2 | Aniline | *p*-$(CH_3)Ph_3$- | β-5.2 | 77 | 82:18 |
| 5.3 | 1-Naphthylamine | Ph- | β-5.3 | 92 | 100:0 |
| 5.4 | 2-Hydroxyl-4-phenylaniline | Ph- | β-5.4 | 91 | 90:10 |
| 5.5 | *N,N*-Diphenyl aniline | Ph- | β-5.5 | 74 | 100:0 |
| 5.6 | *N*-Methylaniline | Ph- | β-5.6 | 93 | 98:2 |
| 5.7 | 2,4-Dimethylaniline | Ph- | β-5.7 | 96 | 98:2 |
| 5.8 | *p*-Chloroaniline | Ph- | β-5.8 | 93 | 100:0 |

General reaction conditions: $Pd(OAc)_2$ (0.02 mmol), dppp (0.04 mmol), aniline & 1-heptyne (2.0 mmol), 120°C, THF (10 ml), 3h, *p*-TsOH (0.12 mmol), 120°C, (a) Isolated total yield (2.1 + 2.2) (b) Determined by GC and $^1H$ NMR.

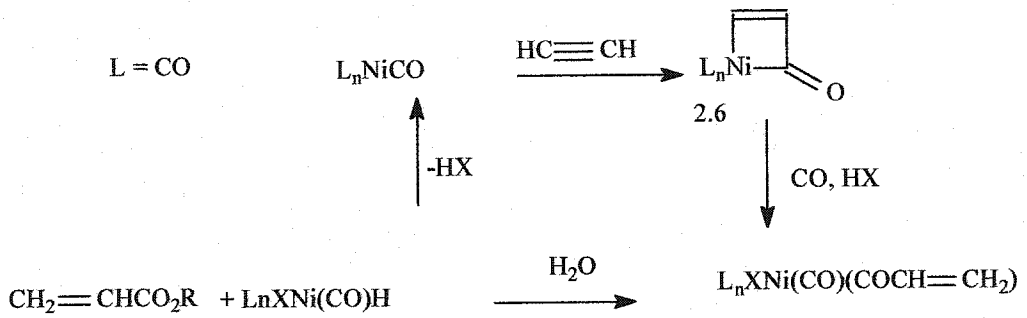
### 2.2.12 Reaction mechanism for gem-α,β-unsaturated acids and derivatives

The mechanisms of the carbonylation of acetylenic substrates are not yet totally understood and it is very difficult to accommodate all the experimental data in a single path. The first mechanism proposed by Reppe (Scheme 7) suggested the formation of ketene intermediate **(2.5)** from the reaction of acetylene with CO, followed by the hydrolysis to yield the product. Reppe later discarded this mechanism soon after the discovery of hydrocarboxylation of the internal alkynes [2].



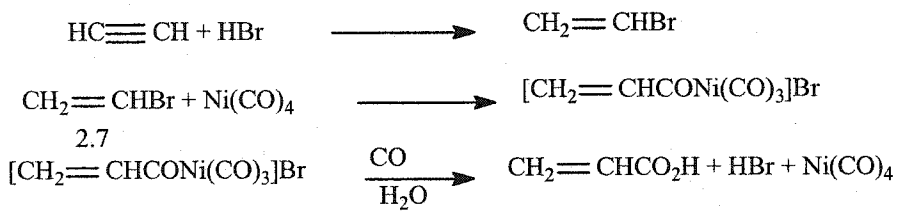

Scheme 7

A second mechanism involves the insertion of coordinated acetylene into Ni-CO to form metallacyclobutenone intermediate **(2.6)**, which then hydrolyzed by $HCl/H_2O$ to furnish the products (Scheme 8) [37]. Few examples of such intermediates were synthesized by the reaction of cyclopropenone with Fe, Co and Pt compounds [37,105].



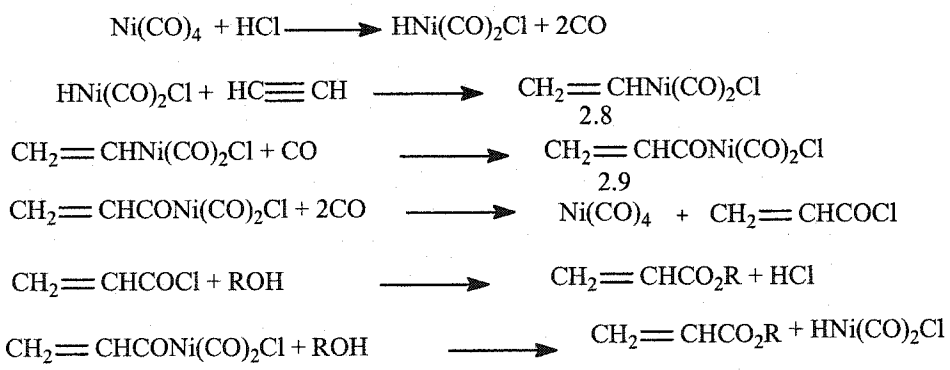

Scheme 8

Later three main pathways for the carbonylation of acetylene using $Ni(CO)_4$/HX were developed. The first involves the activation of acetylene by the addition of HX, followed by the oxidative addition of the vinyl halogenide **(2.7)** to a Ni complex, then CO insertion, and finally hydrolysis to furnish the final products [2,108] (Scheme 9).



Scheme 9

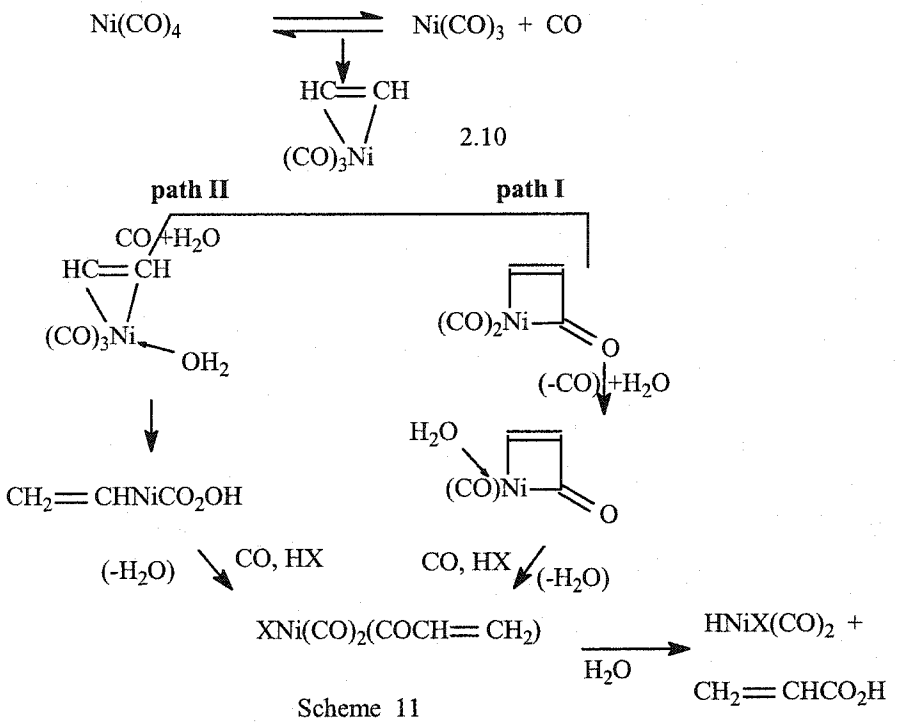
The second pathway involves the formation of a Ni-H species followed by alkyne insertion into the Ni-H forming a nickel alkenyl intermediate **(2.8);** the CO insertion gives acyl species **(2.9)** which then decomposes into final product [109,110] (Scheme 10).



Scheme 10

Finally, a third pathway postulates complexation of acetylene to the nickel atom as the first step. **(2.10)** The complex formed can undergo CO insertion with the formation of a four-membered ring, which is finally cleaved by HX molecule with the formation of an

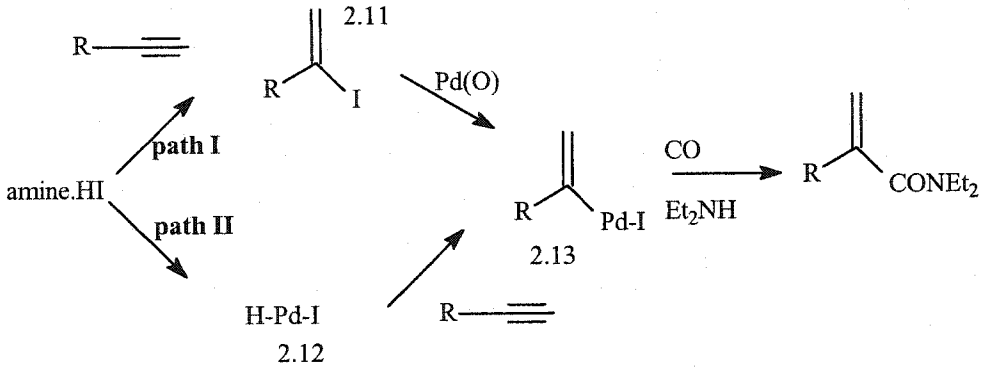
acryloyl nickel derivative (path I). However, if water is present in the complex, an intramolecular protonation of the complex acetylene can take place with formation of a vinyl-nickel complex that undergoes a CO insertion [37] (Scheme 11).




Scheme 11

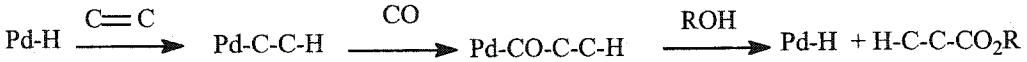
Torri and co-workers [62] proposed two pathways for iodide promoted palladium complex catalyst in the aminocarbonylation of terminal alkynes (Scheme 12). The path I involve the initial addition of HI to acetylene to afford vinyl iodide **(2.11)**, followed by oxidative addition to give **(2.13)**. Another route is an insertion of acetylene to palladium hydride **(2.12)** stemming from Pd(0) and HI. Further conversion of **2.13** to the final product is well established [111,112]. At the end, they concluded that the path II is more

reasonable, because the starting materials were recovered in the absence of Pd catalyst and CO even though stoichiometric amount of iodomethane was used [62].

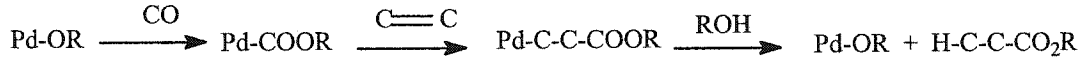



Scheme 12

In carbonylation of alkynes or alkenes using palladium complex catalysts, it is well known that the active species could be either hydride-palladium complex **(2.14)** (metal-hydride mechanism) (Scheme 13), or alkoxy-palladium complex **(2.15)** (metal-alkoxy mechanism) (Scheme 14). The mechanism involving metal-hydride proceeds via insertion of CO into a Pd-alkyl species formed by the addition of olefin to M-H bond and subsequent elimination in the presence of ROH. The mechanism involving metal-alkoxy intermediate involves the insertion of olefin into metal-alkoxy species formed by the addition of ROH to the initially formed metal carbonyl species [46,76,97,98,114].



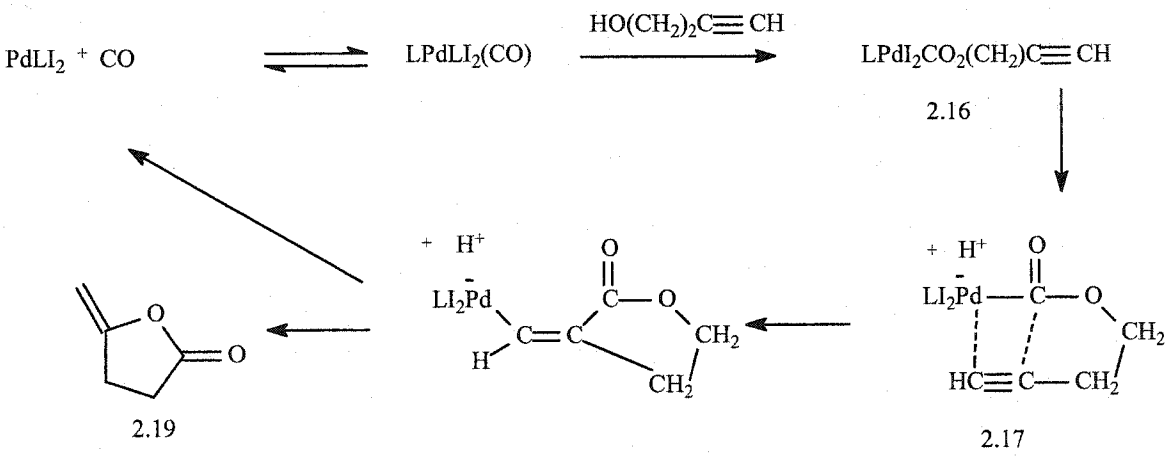

Scheme 13




Scheme 14

Fenton [114], Norton [115], and Drent [46] have endorsed the mechanism involving Pd-COOR or Pd-COOH addition to the alkynes or alkenes. Knifton [47], Tsuji [116], Toniolo [114], Alper [76], Sheldon [117] and Seayad [97] have endorsed the mechanism involving M-H addition to alkenes or alkynes.

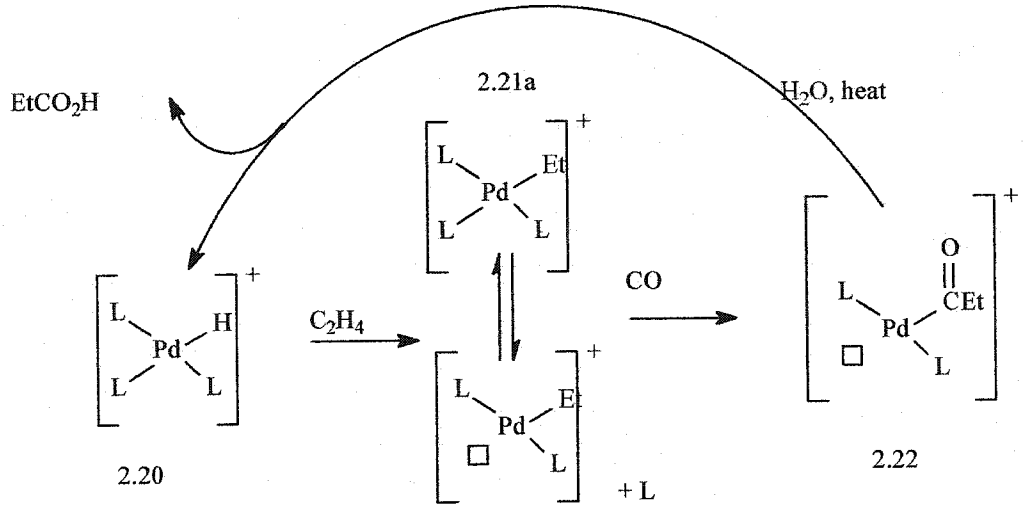
Norton and co-workers have reported a detailed study of the Pd-catalyzed intermolecular cylclocarbonylation of alkynols to methylene lactones. The authors outlined a mechanism of reaction similar to the one presented on Scheme 14: (a) The nucleophilic attack on Pd-CO by -OH of the alkynol forms Pd-$CO_2(CH_2)_2CCH$ **(2.16)**, (b) the intramolecular cycloaddition of the triple bond to the Pd-$CO_2R$ gives the alkenyl intermediate **(2.17)**, and (c) the protic cleavage of **(2.18)** forms the methylene lactone **(2.19)** (Scheme 15).




Scheme 15

Sheldon [117] and co-worker reported the NMR monitored hydrocarboxylation of ethene with cationic palladium hydride **(2.20)**. The initial step is the formation of Pd-alkyl intermediate **(2.21)**, followed by CO insertion to form acyl complex **(2.22)** and finally, hydrolysis at elevated temperature to yield the final product (Scheme 16). Solvent

molecules or anions occupy the vacant orbital. Addition of ten equivalent of TPPTS to **2.22** did not result into the coordination of the fourth ligand.




Scheme 16

### 2.2.13 The mechanism proposed for the system: $Pd(OAc)_2$/dppp/CO/*p*-TsOH

On the basis of the analysis of literatures and experimental observations we are propose a hydride mechanism for the following reasons:

a) The catalytic activity was enhanced in the presence of $H_2$ or acids; especially those acids that contain traces of water, accelerate the formation of Pd-H through water gas shift reaction (Section 2.2.7 and Scheme 3) [97,114].

b) No ester was formed when $[(Ph_3P)_2Pd(Cl)(COOMe)$ was treated with 1-hexene under the catalytic conditions in the absence of CO [116].

c) The addition of acetylene to $[(Cy_3P)_2Pd(H)(HNPh)]$ [118] yielded hydrido alkynyl complex, $[(Cy_3P)Pd(H)(CCH)]$, and aniline, which indicates that the initial

addition of amine (which form the basis of Pd-alkoxy mechanism) in the presence of alkynes is unlikely to take place first.

d) When $Pd(OAc)_2/PPh_3/p$-TsOH was used as catalytic system, a cationic species such as $[HPd(PPh_3)_3]^+OTs^-$ or $[Pd(COOR)(PPh_3)_3]^+OTs^-$ may be formed as the active catalytic species. Under acidic conditions [98] it is reasonable to assume that the hydride species are formed as the major catalytic species.

e) The formation of cationic hydride has been confirmed by isolation and characterization from the stoichiometric reaction of $Pd(OAc)_2$, $PPh_3$ and piperidine carboxylic acid [98]. Similarly, stoichiometric amount of $p$-TsOH, $Pd(OAc)_2$, and TPPTS in aqueous trifloroacetic acid also yield $[Pd(H)(TPPTS)_3]^+$. The hydrocarboxylation reaction with this complex was monitored with NMR spectroscopy [117].

f) In neutral or basic solutions, or in the presence of strongly coordinating anion, (Table 1 and 2, entries 1.2, 1.3, 1.4, 1.10, 2.7 and 2.8) little carbonylation take place, due to probably the absence of the initial hydride complex [117,118].

g) The addition of strongly coordinating anions (e.g. $Cl^-$) to the solution containing Pd-H caused an immediate decomposition of the hydride, accompanied by the evolution of $H_2$ [117].

h) A deuterated acid gave traces of deuterated products; which was confirmed by comparing the integration of methylene protons to that of geminal protons.

### 2.2.14 Steps for the proposed mechanism

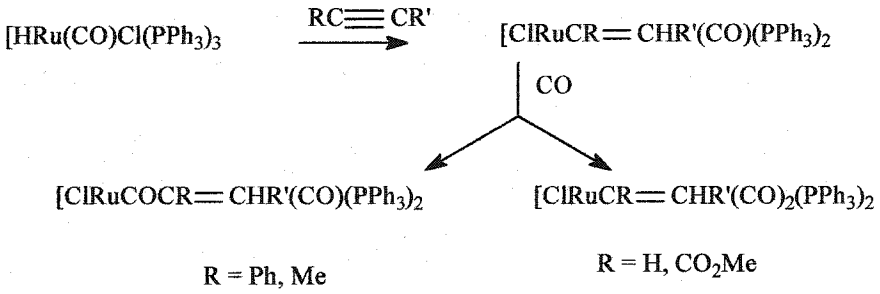
**Step 1.** The first step involves the reaction of the ligand to with $Pd(OAc)_2$ to form $Pd(OAc)_2$(dppp) complex **(2.23)**, this complex has been isolated and characterized as white crystalline solid. The subsequent displacement of acetate ion by the p-TsOH gives a complex [PdH(OTs)(dppp)] [97] **(2.24)**.

Step II. The conversion of **2.24** to active catalytic palladium hydride species **(2.25),** where $OTs^-$ acts as counter anion, is well known in the literature [97,98] and it is a very important step in the carbonylation reaction (Section 2.2.7, Scheme 6).

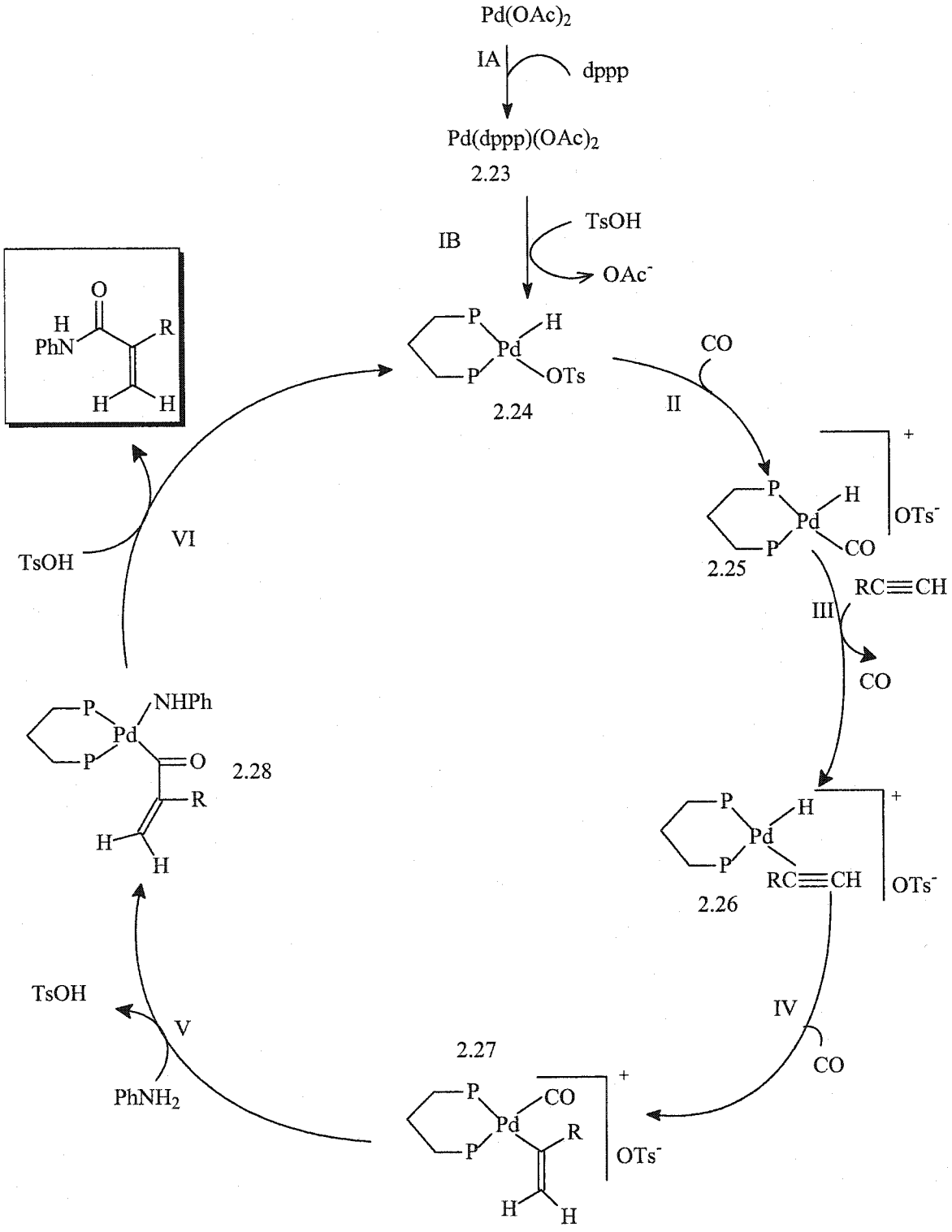
**Step III.** The next step is the π-coordination of alkyne to generate hydrido (alkyne) intermediate **(2.26)** this is made possibly because of strong nucleophilic nature of alkynes [79].

**Step IV.** The complex **(2.26)** undergoes a 1,2-addition (insertion) to the triple bond of the alkyne to form an alkenyl ligand. This step decides the *regiochemistry* of the reaction (Section 2.4.2).

**Step V.** The alkenyl ligand **(2.27)** undergoes migratory insertion into Pd-carbonyl bond to give a Pd-acyl complex **(2.28)**. This sequence of reactions has been reported by Ros [119] for $HRu(CO)Cl(PPh_3)_3$ catalyzed carbonylation of alkynes (Scheme 17).




Scheme 17




Scheme 18. Proposed mechanism for $Pd(OAc)_2$/dppp/CO/*p*-TsOH system

**Step VI.** The final step includes the reductive elimination in the presence of *p*-TsOH to produce the final product *gem*-$\alpha,\beta$-unsaturated amides and to regenerate the catalyst **(2.24)** [113].

### 2.2.15 Factors that control regiochemistry of the reaction

The regiochemistry of the reaction is decided in step IV of the proposed reaction mechanism. These types of hydride additions, and the analogous alkyl additions, have been extensively studied for the past 30 years [35,118]. Evidently, the addition takes place by electron-transfer mechanism, *via* a radical pathway, or bipolar *cis-trans* mechanism. The addition can be concerted depending on the specific catalyst and the reaction conditions. The stereochemistry of the addition is governed by a number of variables, such as the steric hindrance around the metal center (especially with a bulky ligand), electronic nature of the palladium center (including the electronic nature of the ligand), steric and electronic nature of alkynes.

The complete *regioselectivity* was demonstrated by the insertion of phenylacetylene leading exclusively to one product obtained from the palladium center attached to the more reactive carbon atom (internal carbon) regardless of the steric crowdedness around the metal [120] (Table 5, entries 5.1-5.8). Despite the little steric hindrance around the palladium metal the *trans* isomer was minor, we suggest that electronic effects controlled the hydropalladation of alkynes. Similarly, the addition of [Pd] to the more sterically hindered carbon of the triple bond was also reported for alkyl alkynes, especially, when there is a little steric crowdedness around palladium catalyst [120]. However, the steric crowdedness around the metal lead to the converse results, i.e.

the palladium center will be attached to the less crowded carbon atom (Figure 2.2 and 2.3) leading to *trans* isomer [120].

## 2.3 Conclusion

Various *gem*-$\alpha,\beta$-unsaturated amides have been synthesized by carbonylative coupling of terminal alkynes with aniline derivatives using $Pd(OAc)_2$/dppp/$CO/H^+$ catalytic system. In catalytic this catalytic system, both steric and electronic effects of the ligand and that of the substrate affect the regioselectivity of the reaction, but the electronic effect seems to be a predominate factor.

# CHAPTER 3

## TRANSITION METAL CATALYZED CARBONYLATIVE COUPLING OF 1-ALKYNES WITH ANILINE DERIVATIVES TO *TRANS*-$\alpha,\beta$-UNSATURATED AMIDES

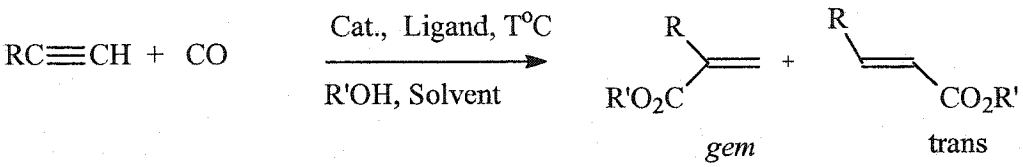
### 3.1 Introduction

The synthesis of *trans*-$\alpha,\beta$-unsaturated amides (linear isomers) was performed by the direct carbonylation of terminal alkynes with aniline derivatives. The linear isomer is formed when hydrogen is attached to the internal carbon of 1-alkynes (more crowded acetylenic carbon) and the amide (-CONHR) is bonded to the terminal (less crowded acetylenic carbon).

Generally, the catalytic systems that afford *trans* esters as the major product of carbonylation terminal alkynes are few (Table 6). These catalytic systems, shown in Table 6, can be grouped into two sets: the first set (Table 6, entries 6.1, 6.2), includes $SnCl_2$ as a co-catalyst (which generate $SnCl_3^-$ ), and the second set (Table 6, entries 6.2-6.6) used dppb as ligand. In both cases the regioselectivity for the *trans* isomer is believed to be controlled by the coordination of sterically hindered ligand (dppb) and the co-catalyst ($SnCl_3^-$) to the central metal.

The catalytic system that we propose consists of CO, hydrogen, dppb, and $Pd(OAc)_2$ (*trans* conditions). $Pd(OAc)_2$ and ligand were added separately to the reaction mixture. The catalytic complex was generated *in situ*. To determine the most suitable reaction conditions, 1-heptyne and aniline were used as model substrates.

**TABLE 6: Catalytic syntheses of *trans*-$\alpha,\beta$-unsaturated esters**




eq 3.1

| Entry | Catalytic systems | Conditions | Alkynes R- | Yield [a] % | Selec. [b] % *trans* | Ref. |
|---|---|---|---|---|---|---|
| 6.1 | $[PR_3PdCl_2]$-$SnCl_2$ | 80° /MIK[c]/6h/ CO (240 atm) | $CH_3(CH_2)_4$- | 65 | 81 | 47 |
| | | | $(CH_3)_3C$- | 30 | 99 | |
| 6.2 | $PtCl_2$(dppb)/$SnCl_2$ | 100°C/22h/THF/ CO (100 atm) | Ph- | 40 | 71 | 49 |
| | | | $CH_3(CH_2)_4$- | 50 | 100 | |
| 6.3 | $Pd(OAc)_2$/dppb/$PPh_3$/*p*-TsOH | 100°C/48h/THF/ CO (100 atm) | $(CH_3)_3C$- | 57 | 60 | 41 |
| | | | $(CH_3)_3Si$- | 55 | 100 | |
| 6.4 | $Pd(OAc)_2$/dppb/$PPh_3$/$HCO_2H$ | 100°C/48h/DME/ CO (100 atm) | $(CH_3)_3C$- | 76 | 79 | 35, |
| | | | $(CH_3)_3Si$- | 65 | 10 | 76 |
| 6.5[d] | $Pd(dba)_2$/dppb | 100°C/4860h/Tol. /CO (80atm) | $CH_3(CH_2)_5$- | 44 | 44 | 48 |
| | | | Ph- | 11 | 11 | |
| 5.6 | $[Pd(dppb)PhCN)_2](BF_4)_2$ | 120°C/6h/MeCN/ CO (40 atm) | Ph- | 35 | 81 | 40 |
| | | | $CH_3(CH_2)_5$- | 44 | 76 | |

a) Total yield for *trans* and *gem* the isomers (b) selectivity for *trans* isomer (c) MIK is methyl isobutyl ketone (d) different organic acids were used in place of methanol and only one product was formed.

In this section we report the first examples of palladium-catalyzed regioselective carbonylation of terminal alkynes with aniline derivatives to produce *trans*-$\alpha,\beta$-unsaturated amides as the major products.

## 3.2 Results and discussion

### 3.2.1 Effect of phosphine ligands

Palladium catalysts used in the carbonylation of 1-heptyne with aniline required an appropriate phosphine ligand for stabilization. The absence of the ligand results in the precipitation of the catalyst as an inactive metal. The role of the ligand, therefore, is to stabilize the molecular palladium species, probably, the zero valence species, which is assumed to be formed when Pd(II) is heated under CO atmosphere [96].

The effect of ligands on the yield and the selectivity toward the *trans* isomer was investigated, seven different bidentate ligands with wide range of bite angles were used in this study: dppe 85° (3.1), dppp 91° (4.0), binap 92° (2.6), dppf 96° (4.3), dppb 98° (5.2), DIOP 98° (4.7) and dpppt. The values in bracket represent the range of bite angles accessible within < 3 kcal additional calculated strain energy. The results summarized in the Figure 3.1 showed an increase in the yield and the selectivity toward *trans*-$\alpha,\beta$-unsaturated amides with the increase in ligand bite angle; the maximum values were obtained with dppb (98°) and then decreased with dpppt. The only exception was observed with binap, which is probably related to the narrow flexibility range and more rigid backbone that reduces the range of bite angle. The decrease in the yield and the selectivity observed with dpppt is probably related to the instability of the bidentate ligand-metal complex presumably formed as intermediate. The use of mixture of dppb

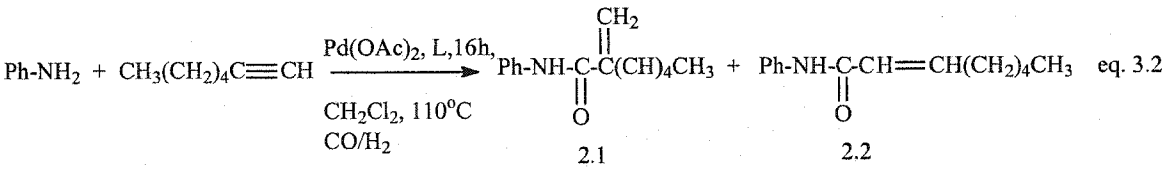
and $PPh_3$, unlike what was observed in hydrocarboxylation of terminal alkynes [35,76], reduced the total yield and the selectivity of the reaction.

The major reasons for this variation in yield and selectivity toward the *trans* isomers are related to both steric and electronic effects of the ligands, with the steric effect seems to be the major determinant in this catalytic system. The steric nature of the catalytic intermediate ensures that the hydropalladation process exhibits high *regio-* and *stereo-selectivity,* resulting in *cis*-addition of Pd complex to a less hindered carbon atom, which finally yields the *trans* product.

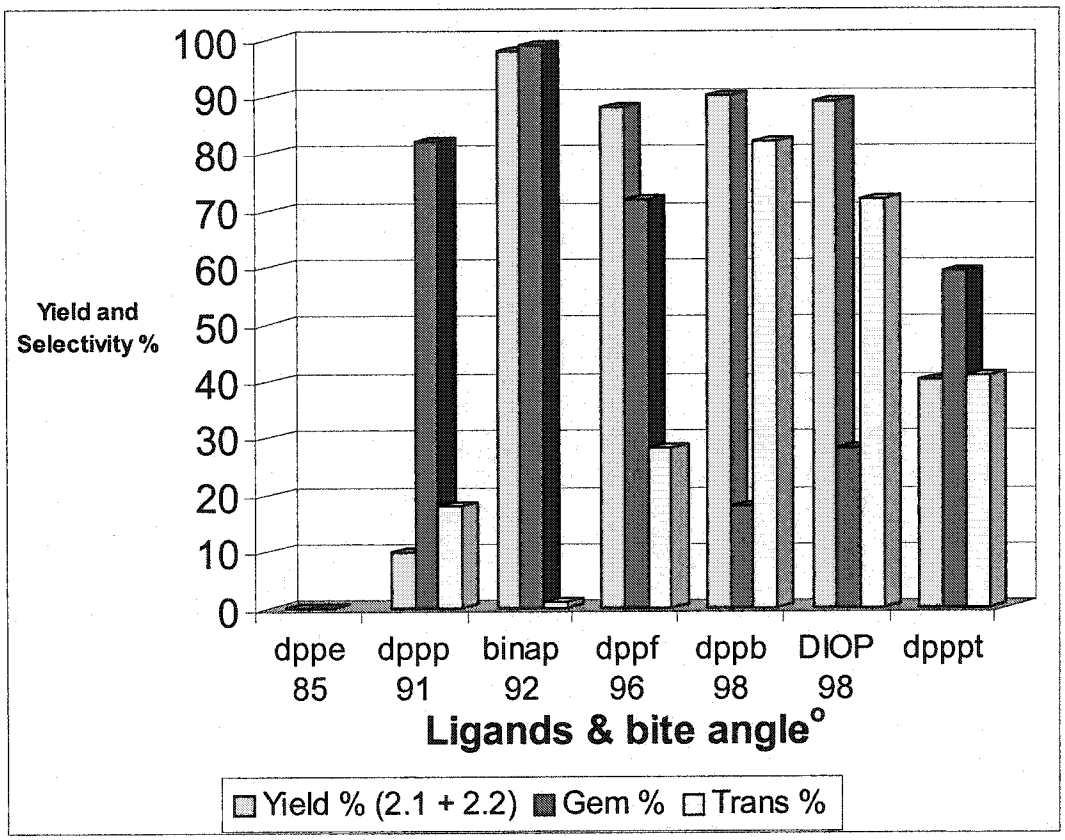
Although there are no data available concerning the basicity of the bidentate ligand from the literature, the following order of the basicity of these three ligands was proposed: DIOP > dppf > binap [121]. Extended Huckel calculation indicates that in the diphosphine complexes with small ligand bite angles the electron density is shifted to the hydride ligand. Therefore, the increase of the bite angle of the ligand increases the hydride ligand acidity [81], hence the basicity of the following ligands increases in the order: dppe > dppp > dppb. This order suggests a possible reason for the reduced activity of dppe. To study the effect of basicity (electronic effect) of the ligand, a more basic ligand (DIOP) with the same bite as dppb was used under the standard reaction conditions; the selectivity of the *trans* isomer dropped by 10%, with no change in the yield of the reaction. This is a clear indication that ligand with moderate basicity dppb is more efficient with respect to selectivity and yield of the *trans*-$\alpha,\beta$-unsaturated amide.

A correlation between the increase in diphosphine ligand bite angles and the rate or selectivity has also been observed in the elimination of RCN from [Pd(R)CN(P-P)]; the

**Carbonylative coupling of 1-heptyne with aniline catalyzed by $Pd(OAc)_2$/ligand/$CO/H_2$; Effect of different diphosphine ligands**




L = dppe, dppp, binap, dppf, dppb, DIOP, dpppt




General reaction conditions: $Pd(OAc)_2$ (0.02 mmol), bidentate ligands (0.08 mmol), aniline & 1-heptyne (2.0 mmol), $CH_2Cl_2$ (10.0 ml), $H_2$ (300 psi), CO (300 psi), 110°C, 16h.

**Figure 3.1**

reaction with DIOP was found to be 10000 times faster than the one with dppe [122]. In 1987 Kodak Eastman patented a BISBI-based rhodium catalyst [2,2'-bis-(diphenylphosphino)methyl)1,1'biphenyl] that yielded a high selectivity towards linear aldehyde. [123]. To explain the high selectivity, Casey and Whiteker [124,125] looked at the bite angles of diphosphine ligands and they found good correlation between the ligand bite angle and the catalyst selectivity.

### 3.2.2 Effect of the different type of palladium catalysts

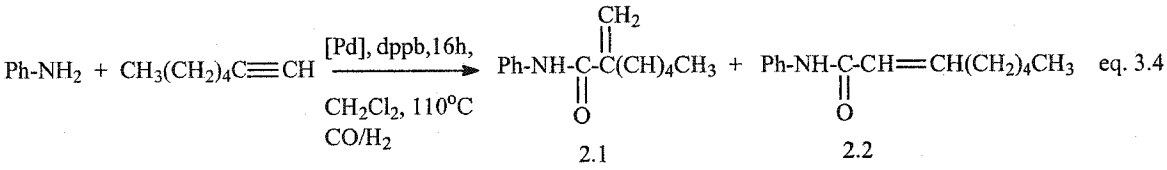
The activity and the selectivity of various palladium catalysts in the catalytic carbonylative coupling of 1-heptyne with aniline are summarized in Table 7. All palladium catalysts containing chloride ions gave lower yields and selectivity of *trans*-$\alpha,\beta$-unsaturated amide compared to $Pd(OAc)_2$. This probably related to the strong interaction of the chloride ion with the active center compared to the relatively easy replacement of $OAc^-$ anion by bidentate phosphine ligand.

Although $Pd(PPh_3)_4$ is slightly less active than $Pd(OAc)_2$, it is nevertheless a good pre-catalyst for the carbonylation reaction. Therefore, Pd(0) species doesn't hinder the catalytic activity significantly. The result is not surprising because Pd(II) has been known to undergoes *in situ* reduction to Pd(0) under CO pressure [96] eq. 3.2.

$$Pd(OAc)_2 + CO \xrightarrow[\text{heat}]{} Pd + (Ac)_2O + CO_2 \qquad \text{eq. 3.3}$$

A heterogeneous catalyst precursor such as Pd/C does not catalyze the reaction of carbonylation in the absence of phosphine ligand [76]. Interestingly, the presence of a

**TABLE 7. Carbonylative coupling of 1-heptyne with aniline catalyzed by [Pd]/dppb/CO/$H_2$; Effect of other palladium catalysts**




| Entry | Catalyst | Yield %[a] | Selectivity %[b] *2.1:2.2* |
|---|---|---|---|
| 7.1 | $Pd(OAc)_2$ | 90 | 18:82 |
| 7.2 | $Pd(PPh_3)_4$ | 80 | 28:72 |
| 7.3 | $PdCl_2(PPh_3)_2$ | 64 | 26:74 |
| 7.4 | Pd/C 10% | 61 | 24:76 |
| 7.5 | $PdCl_2$ | 57 | 26:74 |
| 7.6 | $PdCl_2(PhCN)_2$ | 45 | 27:73 |
| 7.7[c] | $Pd(OAc)_2$(dppb) | 41 | 42:58 |

General reaction condition: [Pd] (0.02 mmol), dppb (0.08 mmol), aniline & 1-heptyne (2.0 mmol), $CH_2Cl_2$ (10.0 ml), $H_2$ (300 psi), CO (300 psi), 110°C, 16h (a) Isolated yield 2.1 + 2.2 (b) Determined by GC and $^1$HNMR (c) no extra ligand was used.

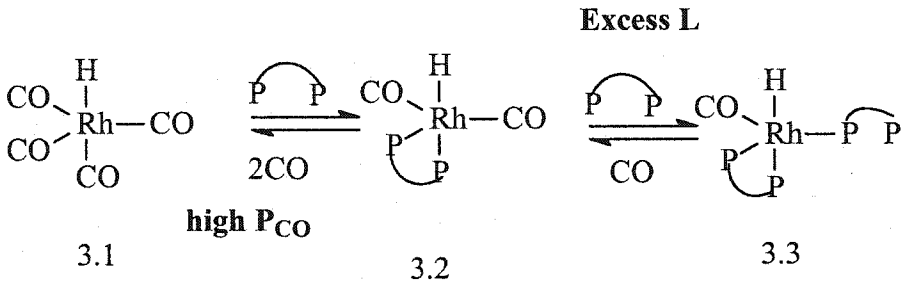
suitable phosphine ligand increases the carbonylation activity of the Pd/C (Table 7, entry 7.4). This can be simply explained by the leaching of palladium from the heterogeneous surface to the solution, which in contact with the phosphine ligand to form the active catalyst. The fact that Pd/C catalyzed the carbonylative coupling of alkynes with aniline suggests that the catalytic active specie is not necessarily only Pd(II), but it can be either Pd(0) or Pd(II).

The activity and the selectivity of other tested palladium catalysts toward the formation of *trans* isomer **(2.2)** are lower than $Pd(OAc)_2$ due to the presence of $PPh_3$, which has been known to increase the selectivity of *gem* **(2.1)** [20], or the lack of weakly coordinate ion such as $OAc^-$ that acts as counter ion (Table 7, entry 7.2) and also due to the presence of $Cl^-$. (Table 7, entries 7.3, 7.5 and 7.6).

### 3.2.3 Effect of ligand to catalyst ratio

The significant influence of the molar ratio of dppb ligand to palladium catalyst on the yield and the selectivity of carbonylative coupling of 1-heptyne with aniline were examined (Figure 3.2). The effect of this ratio is more noticeable with $Pd(OAc)_2$/dppb/$CO/H_2$ catalytic system than with $Pd(OAc)_2$/dppp/$CO/H^+$ due to the excess of the ligand needed to stabilize the presumed Pd(0) intermediate. The highest yield of products and the selectivity toward the *trans* isomer showed maximum value at the molar ratio of ligand to catalyst equal to four, and then these value decreased as the dppb was further added. Precipitation of metallic palladium was observed at dppb/[Pd] molar ratio of two and less.

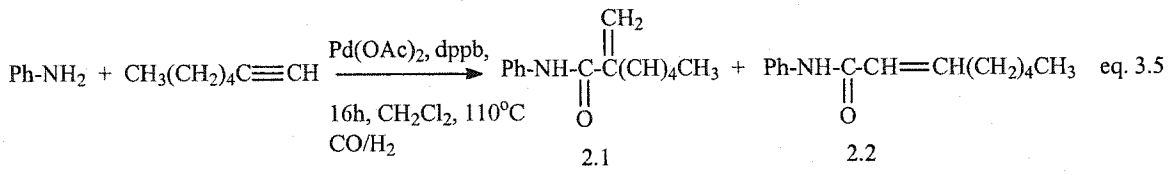
The effect of increasing the amount of ligand upon the reaction rate is usually flattened above certain concentration [126]. A six-fold excess of phosphine over [Pd] practically kills the catalysis in Heck reaction [127]. The drop in yield at molar ratio greater than four could be related to the blockage of the substrate coordination by the excess ligand.



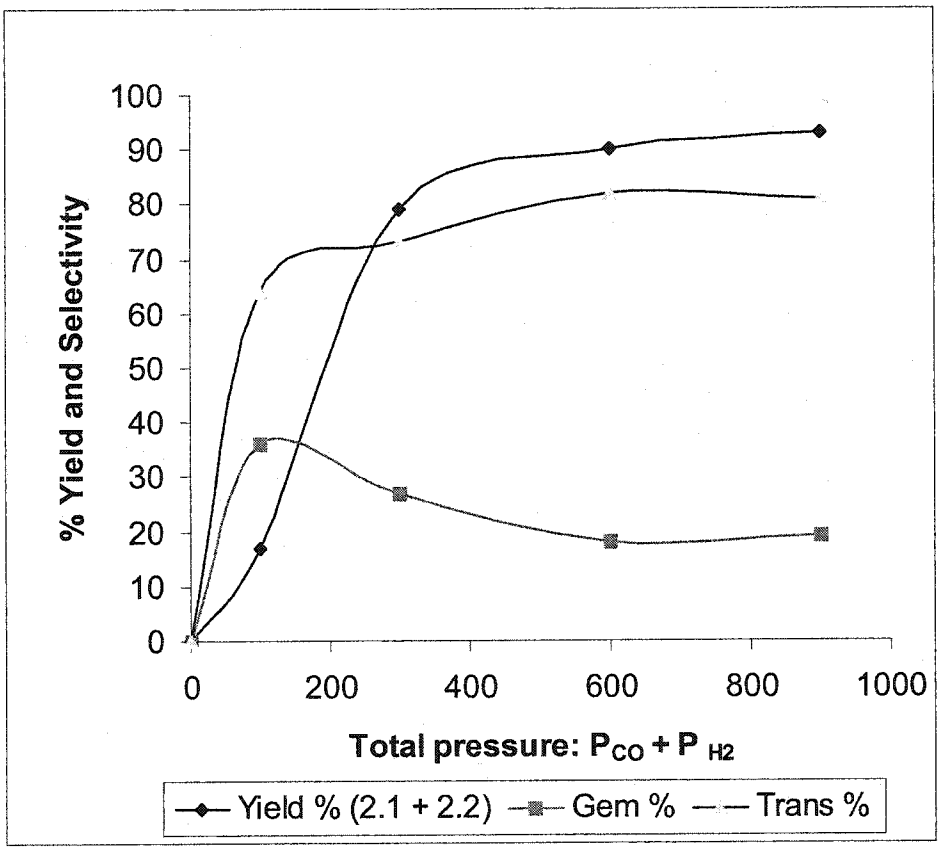

Scheme 19

What is the role of the excess phosphine ligand, other than the stabilization of the catalyst and the formation of the more steric crowdedness around the palladium center? Why molar ratio 4 rather than the optimum molar ratio (2) with $Pd(OAc)_2$/dppp/CO/$H^+$ catalytic system is needed? This can be understood if we look at the following equilibrium among the species formed by rhodium-diphosphine catalysts [128] (Scheme 19). At high syngas pressure and low ligand concentration CO occupied most of the coordination sites **(3.1)**, and the equilibrium will move to the left. It is unlikely that species **3.1** is involved in catalytic process. The higher syngas pressure of 600 psi used with $Pd(OAc)_2$/dppb/CO/$H_2$ system compared to 100 psi in $Pd(OAc)_2$/dppp/CO/$H^+$ catalytic system may explain the reason of the excess ligand required to shift the equilibrium to the right.

**Carbonylative coupling of 1-heptyne with aniline catalyzed by $Pd(OAc)_2$/dppb/$CO/H_2$; Effect of dppp/[Pd]**



eq. 3.5




General reaction conditions: $Pd(OAc)_2$ (0.02 mmol), dppb (0-0.16 mmol), aniline & 1-heptyne (2.0 mmol), $CH_2Cl_2$ (10.0 ml), $H_2$ (300 psi), CO (300 psi), 110°C, 16h.

**Figure 3.2**

It has been reported that for rhodium catalyst containing the chiral 2,4-bis(diphenylphosphino)pentane(dpppt) ligand the enantioselectivity heavily depends on the ligands to metal molar ratio and the optimum ratio was four [129]. A $Pd(OAc)_2$:$PPh_3$:dppb ratio of 1:4:2 was found as the optimum ratio in the hydrocarboxylation of alkynes [35]. Similarly, the deactivation of the catalyst was less significant under the reaction conditions of Pd(OAc):$PPh_3$:pyca:*p*-TsOH (1:30:15:40) [98]. In hydroformylation of styrene the selectivity toward linear aldehydes and ligand to catalyst ratio depend mainly on the type of ligand; for example, dppe/[Rh] ≥2 decreases the selectivity whereas dppp/[Rh] ≥2 increases the selectivity toward the *trans* [128] aldehydes.

### 3.2.4 Effect of the pressure CO and $H_2$

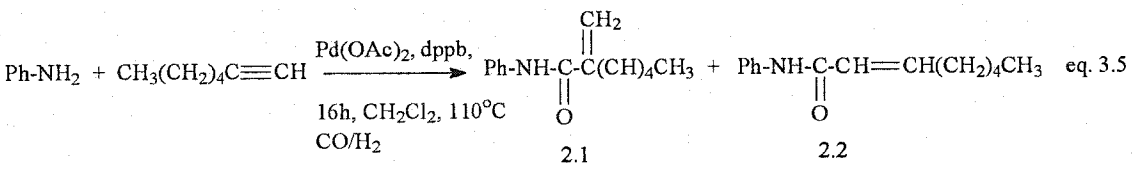
#### 3.2.4.1 Effect of total pressure (CO:$H_2$ = 1:1)

In carbonylation reaction, a minimum pressure of CO and hydrogen is needed to dissolve sufficient amount of these gases in the reaction medium [76]. Figure 3.3 summarized the effect of the total pressure (CO: $H_2$ = 1:1) on the yield and the selectivity of the reaction. The increase in the total pressure increases the yield and the selectivity toward *trans*-$\alpha,\beta$-unsaturated amide **(2.2)**. The difference in yields obtained at 600 psi and 900 psi were not significant, therefore, a pressure of 600 psi was adopted.

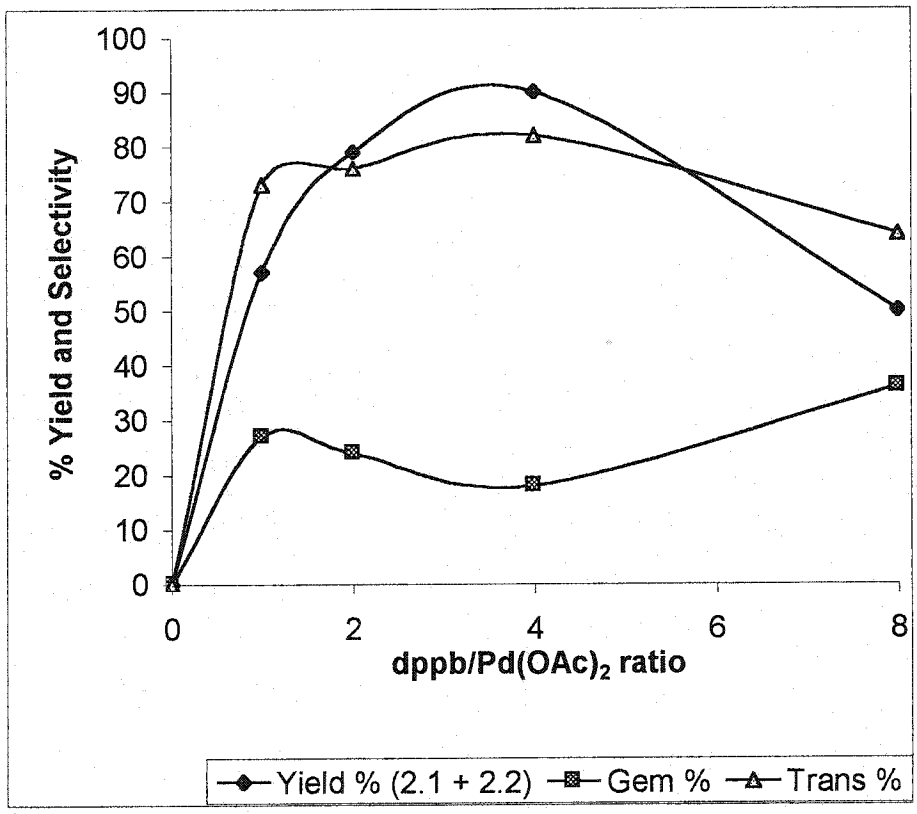
#### 3.2.4.2 Effect of the ratio of partial pressures CO:$H_2$

The ratio of the partial pressure of CO and $H_2$ affects to certain extents the regioselectivity of the carbonylation reaction. Figure 3.4 shows the result of the effect of CO:$H_2$ ratio on

**Carbonylative coupling of 1-heptyne with aniline catalyzed by $Pd(OAc)_2$/dppb/$CO/H_2$; Effect of the total pressure CO and $H_2$**



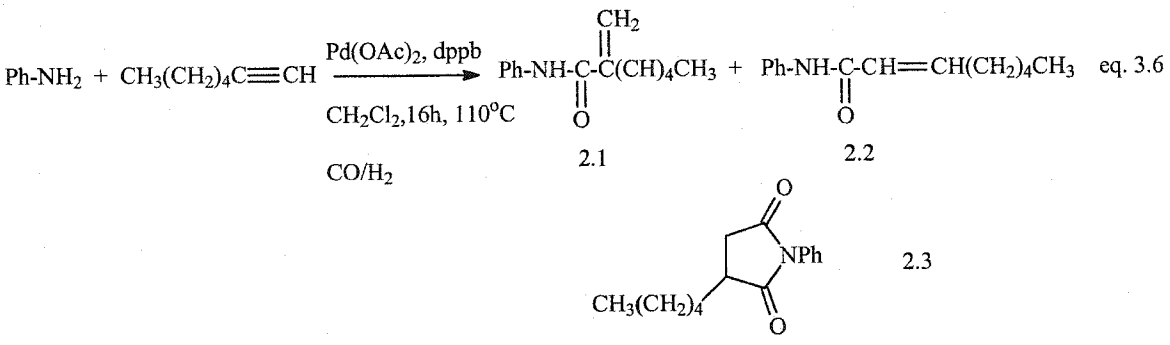

eq. 3.5

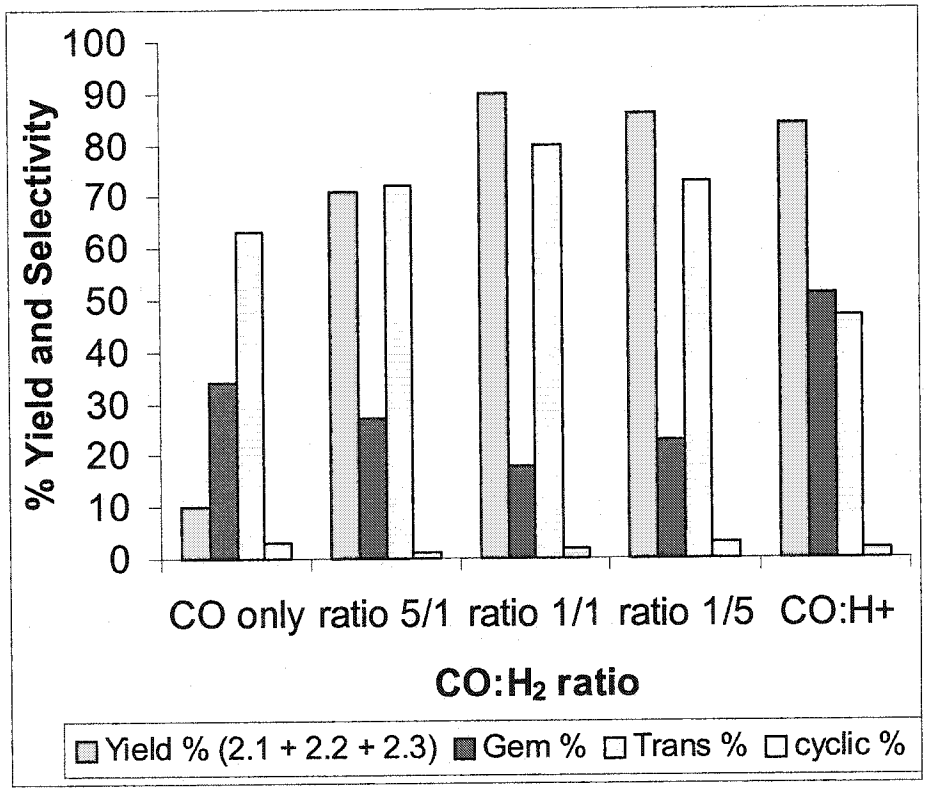



General reaction conditions: $Pd(OAc)_2$ (0.02 mmol), dppb (0.08 mmol), aniline & 1-heptyne (2.0 mmol), $CH_2Cl_2$ (10.0 ml), $P_{CO} + P_{H2}$ (100-900 psi 1:1), 110°C, 16h.

**Figure 3.3**

**Carbonylative coupling of 1-heptyne with aniline catalyzed by $Pd(OAc)_2$/dppb/$CO/H_2$; Effect of the ratio of partial pressure of $CO:H_2$**




General reaction conditions: $Pd(OAc)_2$ (0.02 mmol), dppb (0.04 mmol), aniline & 1-heptyne (2.0 mmol), $CH_2Cl_2$ (10.0 ml), $CO:H_2$ 600 psi (5/1,1/1,1/5), 110°C, 16h.

**Figure 3.4**

both the rate and the composition of the isomers. Less than 10% of isolated yield of the amide products were obtained in the absence of hydrogen. Also the use of *p*-TsOH in place of hydrogen decreases the yield to 84% and changes the selectivity of the reaction in favor of the *gem* isomer (*gem:trans:cyclic* 51:47:2 respectively).

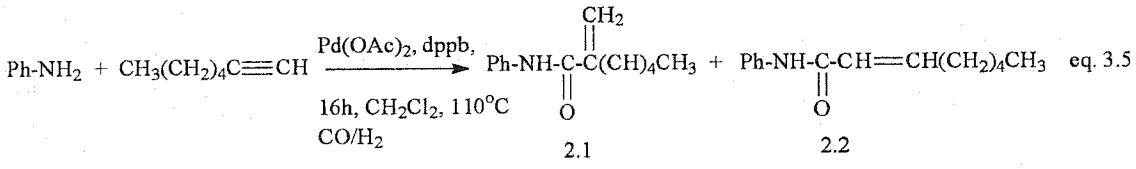
Generally, the decrease of the ratio of $CO:H_2$ increases the total yield and the selectivity. The lowest yield was obtained at $CO/H_2$ ratio of 5/1. From these results, it can be inferred that (a) the possible reaction mechanism with $Pd(OAc)_2/CO/H_2$ system is probably the same as $Pd(OAc)_2/CO/H^+$ system i.e. via Pd-H, (b) the presence of acid increases the selectivity toward the formation of *gem* isomer

(c) hydrogen is needed to enhance the activity of the reaction. The little change in rate of the reaction between ratio 1/1 and 1/5, coupled with the desire for the quantitative exploitation of the syngas, means that the ratio of 1:1 has to be used to avoid excessive hydrogenation that may occur at 1/5 ratio.

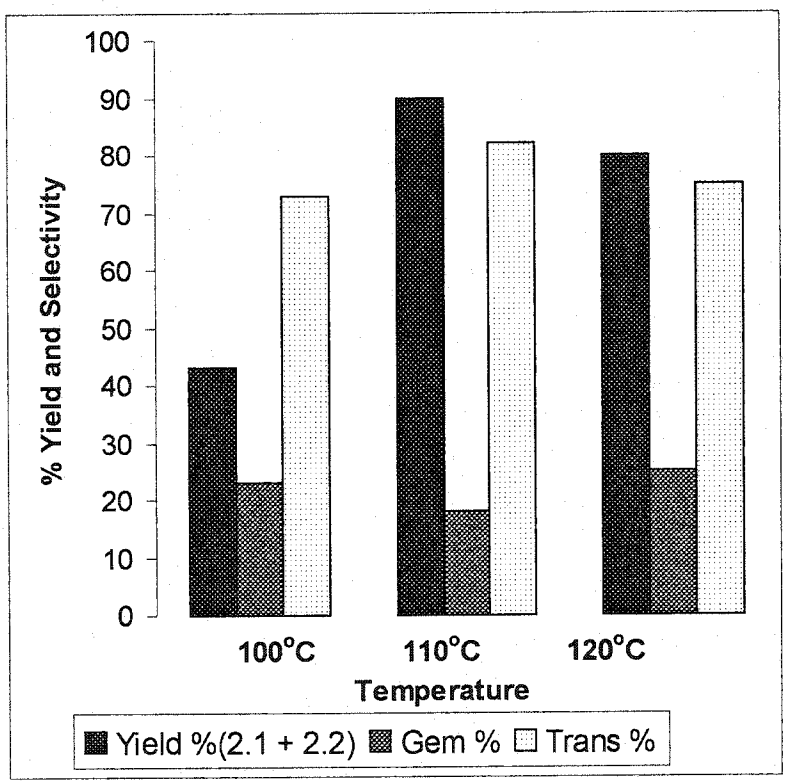
### 3.2.5 Effect of temperature

The effect of the reaction temperature on the yield and the selectivity of carbonylative addition of aniline to 1-heptyne have been studied (Figure 3.5). The optimum temperature is 110°C; higher temperature resulted in lower yield, due to the hydrogenation and isomerization of the $\alpha,\beta$-unsaturated amide, as well as the formation of metallic palladium from palladium catalyst, especially Pd(0) [43]. Both conversion and selectivity toward the *trans*-$\alpha$,β-unsaturated amide **(2.2)** was deteriorated as the reaction temperature decreased.

**Carbonylative coupling of 1-heptyne with aniline catalyzed by $Pd(OAc)_2$/dppb/$CO/H_2$; Effect of temperature**




eq. 3.5




General reaction conditions: $Pd(OAc)_2$ (0.02 mmol), dppb (0.08 mmol), aniline & 1-heptyne (2.0 mmol), $CH_2Cl_2$ (10.0 ml), $H_2$ (300 psi), CO (300 psi), 100-120°C,16h.

**Figure 3.5**

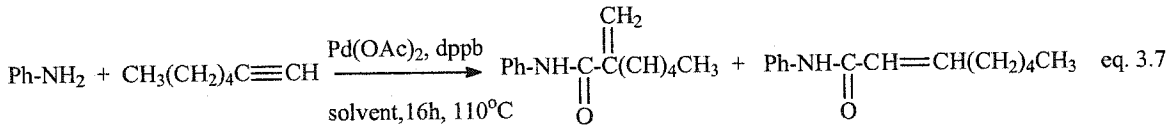
Detailed kinetic studies revealed an intrinsic deactivation process of the standard phosphine-palladium catalyst employed in Heck coupling reactions, which suffered from phosphorous-carbon bond cleavage, that seems to increase with temperature [130]. The detrimental consequence of P-C-bond cleavage is the loss of Pd (0)-stabilizing phosphine with formation of palladium black, a notorious disadvantage of palladium-phosphine catalysts in general [131].

### 3.2.6 Effect of solvents

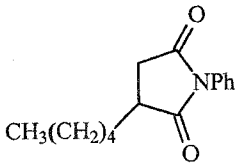
Table 8 contains the results of the effect of various solvents on the catalytic carbonylative coupling of 1-heptyne with aniline. The best solvent term of both yield and selectivity is dichloromethane. All the other solvents gave poor selectivity and yield of $\alpha,\beta$-unsaturated amide. No correlation between the yield, selectivity and dielectric constant of the solvents. Fairly polar THF the solvent of choice with $Pd(OAc)_2$/dppp/CO/$H^+$ catalytic system, gave only traces under the present reaction conditions. Chloroform and toluene gave moderate isolated yield of the products with poor selectivity toward the α,β-unsaturated amide (high selectivity for *gem* and cyclic).

Why is $CH_2Cl_2$ particularly unique for this reaction? Is $CH_2Cl_2$ participating in any of the steps? The answer is still not clear, but it is known that Pd(0) formed from Pd(II) under CO pressure (eq. 3.2) in the absence of strongly coordinating ligand in acetic acid as solvent yields tetranuclear cluster $[Pd(CO)OAc]_4$ [96]. Similarly, the reaction of dinuclear Pd(I) complex $[Pd_2(Cl_2(\mu\text{-dppm})_2]$ with bis(diethylamino)acetylene ($Et_2NCCNEt_2$) in $CH_2Cl_2$ yields substituted benzene derivatives and a methylene bridge

**TABLE 8. Carbonylative coupling of 1-heptyne with aniline catalyzed by $Pd(OAc)_2$/dppb/$CO/H_2$; Effect of solvents.**




Solvents = Tol., THF, $CH_3CN$, $CH_3Cl$, $CH_2Cl_2$




2.3

| Entry | Solvent | Yield[a] % | Selectivity[b] % *2.1:2.2:2.3* |
|---|---|---|---|
| 8.1 | $CH_3Cl$ | 46 | 30:48:22 |
| 8.2 | THF | Traces | - - - |
| 8.3 | $CH_3CN$ | 3 | 100:0:0 |
| 8.4 | $CH_2Cl_2$ | 90 | 18:80:2 |
| 8.5 | Toluene | 40 | 46:34:20 |

General reaction condition: $Pd(OAc)_2$ (0.02 mmol), dppb (0.08 mmol), aniline & 1-heptyne (2.0 mmol), solvents (10.0 ml), $H_2$ (300 psi), CO (300 psi), 110°C, 6h (a) Isolated yield 2.1 + 2.2 + 2.3 (b) Determined by GC and $^1$HNMR.

complex [$Pd_2Cl_2(\mu$-$CH_2$-)($\mu$-dppm)$_2$]; no reaction was observed when chloroform was used in place of $CH_2Cl_2$ [131].

### 3.2.7 Effect of reaction time

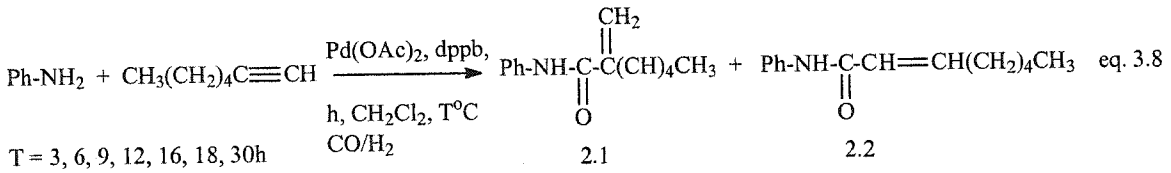
Figure 3.6 contains the results of the effect of varying the reaction time on the yield and selectivity of the catalytic carbonylative coupling of 1-heptyne with aniline. Generally, an increase in reaction time increases the total yield of the reaction. The optimum reaction time is 16 h. Further increase in the time decreases the total yield of the reaction due to the hydrogenation of the products.

The selectivity of the reaction toward *trans* isomer **(2.2)** remained fairly constant throughout the reaction time. From this it can be inferred that the catalytically active species did not evolve during the course of the reaction [128], hence the regioselectivity of the reaction is almost probably determined during the main catalytic cycle and depends on steric and other factors influencing the reaction mechanism. In other words the possibility of an independent isomerization process occurring parallel to the main catalytic process is slim [35].

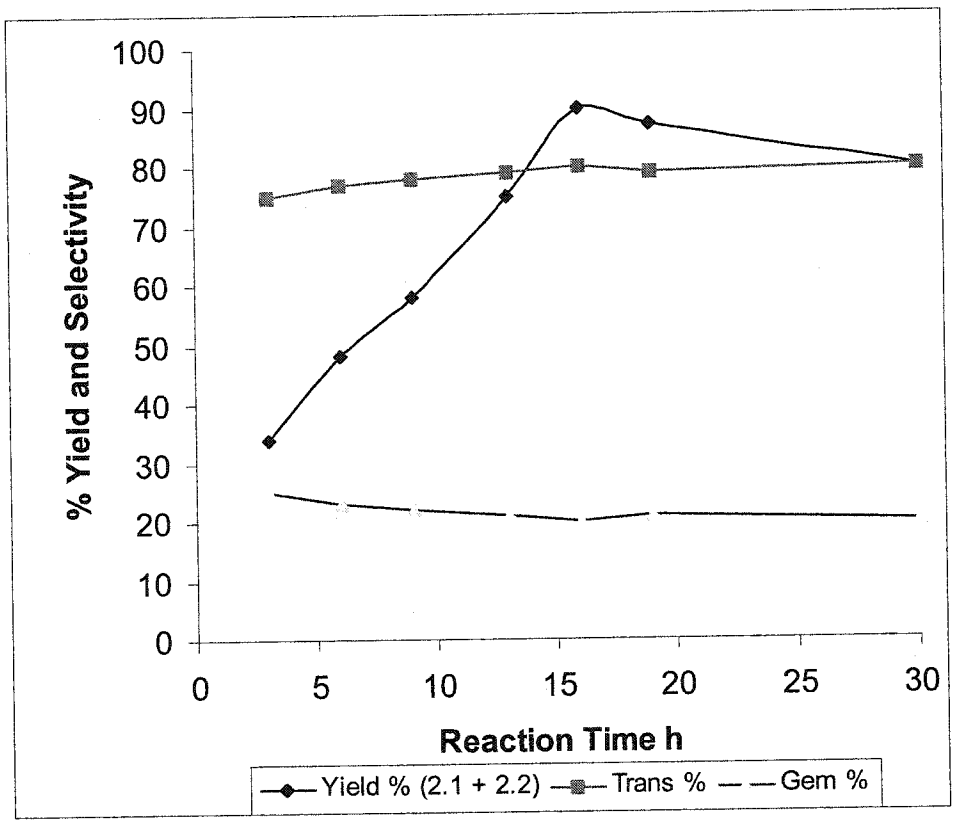
### 3.2.8 Carbonylative coupling of different alkyl alkynes with aniline derivatives catalyzed by $Pd(OAc)_2$/dppb/$CO/H_2$

The carbonylative coupling of different alkyl alkynes with aniline derivatives were carried out with catalytic system that includes $Pd(OAc)_2$/dppb/$CO/H_2$ (standard *trans*

**Carbonylative coupling of 1-heptyne with aniline catalyzed by $Pd(OAc)_2$/dppb/$CO/H_2$; Effect of reaction time**




eq. 3.8




General reaction conditions: $Pd(OAc)_2$ (0.02 mmol), dppb (0.08 mmol), aniline & 1-heptyne (2.0 mmol), $CH_2Cl_2$ (10.0 ml), $H_2$ (300 psi), CO (300 psi), 110°C, 3-30h.

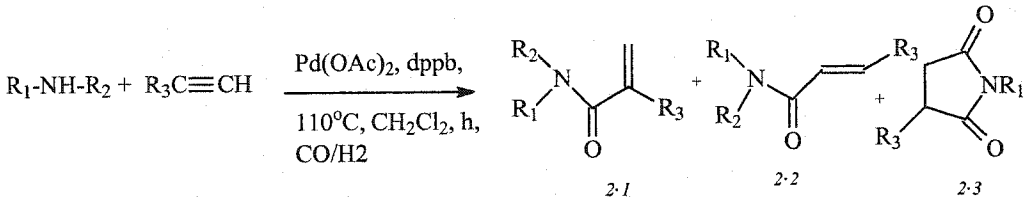
**Figure 3.6**

conditions (Table 9)). Excellent (95-100 %) and good (60-95) selectivity toward *trans* isomers **(2.2)** were obtained by the reaction of 3,3-dimethyl-1-butyne with aniline, *p*-chloroaniline, 2,4-dimethylaniline, *N*-methylaniline, and with 2-aminophenol (Table 9, entries 9.5, 9.10, 9.15, 9.20, 9.25). When 5-hexynenitrile was used in place of 3,3-dimethyl-1-butyne, the selectivity of *trans* isomers dropped significantly (42-71 %)(Table 9, entries 9.1, 9.6, 9.11, 9.16, 9.21).

A combination of steric and electronic factors is believed to contribute to the unique selectivity exhibited by 3,3-dimethyl-1-butyne. The steric effect of tertiary butyl group ($(CH_3)_3C$-) and the ligand (dppb) reduces the chance of addition of palladium center to the internal carbon ($\beta$-carbon) in the hydropalladation process, as a result hydrogen is added to the internal carbon of the triple bond and [Pd] to the terminal carbon, hence *trans* isomer is formed in an excellent yield. The higher nucleophilicity of the $\alpha$-carbon also enhances the addition of hydrogen to it. The lower selectivity obtained with 5-hexynenitrile compared to 3,3-dimethyl-1-butyne is probably related to the less bulkiness of the R- group ($CN(CH_2)_3C$-), and also to the electron withdrawing ability of the cyano group making $\alpha$-carbon relatively more nucleophilic compared to $\beta$-carbon, as the result the hydrogen has greater tendency to attack the terminal carbon ($\alpha$-carbon), hence more *gem* isomer was formed compared to the carbonylation of 3,3-dimethyl-1-butyne.

Earlier works based on nickel catalysts suggested that this addition is mostly directed by the nature of the substituent on the alkyne and it occurs according to Markovnikov type of addition [132]. In contrast, more recent results obtained with

**TABLE 9: Carbonylative coupling of different alkyl alkynes with aniline derivatives catalyzed by $Pd(OAc)_2$/dppb/$CO/H_2$**




eq. 3.9

| Entry | Alkynes $R_3$- | Aniline derivatives | Yield %[a] | *Trans*-prod [b]. | Selectivity %[c] *2.1:2.2:2:3* |
|---|---|---|---|---|---|
| 9.1 | $CN(CH_2)_3$- | Aniline $R_1$= Ph; $R_2$ = H | 62 | α-9.1 | 32:68:0 |
| 9.2 | $CH_3(CH_2)_2$- | | 90 | α-9.2 | 18:70:12 |
| 9.3 | $CH_3(CH_2)_4$- | | 90 | α-9.3 | 17:80:3 |
| 9.4 | $CH_3(CH_2)_6$- | | 82 | α-9.4 | 20:79:1 |
| 9.5 | $(CH_3)_3C$- | | 87 | α-9.5 | 5:95:0 |
| 9.6 | $CN(CH_2)_3$- | *p*-Chloroaniline $R_1$= *p*-$ClC_6H_4$; $R_2$ = H | 89 | α-9.6 | 29:71:0 |
| 9.7 | $CH_3(CH_2)_2$- | | 91 | α-9.7 | 16:84:0 |
| 9.8 | $CH_3(CH_2)_4$- | | 97 | α-9.8 | 11:83:6 |
| 9.9 | $CH_3(CH_2)_6$- | | 78 | α-9.9 | 16:84:0 |
| 9.10 | $(CH_3)_3C$- | | 90 | α-9.9 | 4:96:0 |

| Entry Cont. | 1-alkynes $R_3$- | Aniline derivatives | Yield %[a] | *Trans* prod. [b] | Selectivity %[c] *2.1:2.2:2.3* |
|---|---|---|---|---|---|
| 9.11 | $CN(CH_2)_3$- | 2,4-Dimethylaniline $R_1$=2,4-$(CH_3)_2C_6H_3$; $R_2$ = H | 67 | α-9.11 | 58:42:0 |
| 9.12 | $CH_3(CH_2)_2$- | | 91 | α-9.12 | 28:72:0 |
| 9.13 | $CH_3(CH_2)_4$- | | 68 | α-9.13 | 27:70:3 |
| 9.14 | $CH_3(CH_2)_6$- | | 62 | α-9.14 | 30:70:0 |
| 9.15 | $(CH_3)_3C$- | | 98 | α-9.15 | 2:98:0 |
| 9.16 | $CN(CH_2)_3$- | *N*-Methylaniline $R_1$= Ph; $R_2$ = $CH_3$ | 87 | α-9.16 | 53:47:0 |
| 9.17 | $CH_3(CH_2)_2$- | | 86 | α-9.17 | 31:69:0 |
| 9.18 | $CH_3(CH_2)_4$- | | 95 | α-9.18 | 39:61:0 |
| 9.19 | $CH_3(CH_2)_6$- | | 85 | α-9.19 | 30:70:0 |
| 9.20 | $(CH_3)_3C$- | | 60 | α-9.20 | 0:100:0 |
| 9.21 | $CN(CH_2)_3$- | 2-Aminophenol $R_1$= *o*-OH-$C_6H_4$; $R_2$ = H | 86 | α-9.21 | 31:69:0 |
| 9.22 | $CH_3(CH_2)_2$- | | 85 | α-9.22 | 25:60:15 |
| 9.23 | $CH_3(CH_2)_4$- | | 98 | α-9.23 | 17:56:27 |
| 9.24 | $CH_3(CH_2)_6$- | | 88 | α-9.24 | 15:59:26 |
| 9.25 | $(CH_3)_3C$- | | 88 | α-9.25 | 0:100:0 |

General reaction conditions: $Pd(OAc)_2$ (0.02 mmol), dppb (0.08 mmol), aniline derivatives & 1-alkynes (2.0 mmol), $CH_2Cl_2$ (10.0 ml), $H_2$ (300 psi), CO (300 psi), 110°C , 16h (a) Isolated yield 2.1 + 2.2 + 2.3 (b) Identification number for the major product (c) Determined by GC and $^1$HNMR .

palladium catalysts indicate that the catalytic system is able to almost completely control the regioselectivity of the reaction [42,47,493].

In our present study, it is clear that both the nature of the substituent group of the alkynes and the catalytic system played an important role in the yield and selectivity of the reaction. Generally, the selectivity of the various alkynes toward *trans* isomers decreases by decreasing the bulkiness and electron donating ability of group on the alkyne ($CN(CH_2)_3C$- < $CH_3(CH_2)_2C$- < $CH_3(CH_2)_4C$ -< $CH_3(CH_2)_6C$- < $(CH_3)_3C$-).

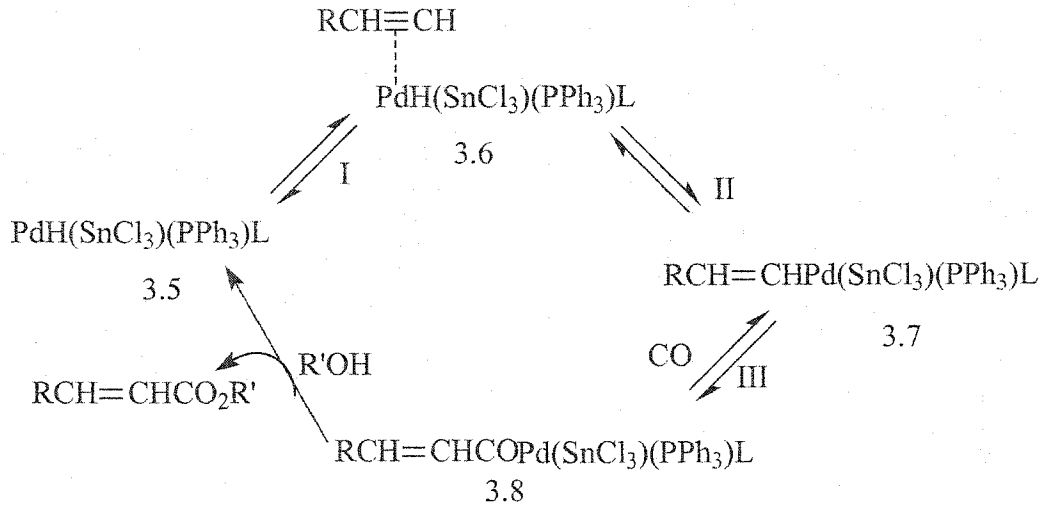
### 3.2.9 Carbonylative coupling of different aryl alkynes with aniline derivatives catalyzed by $Pd(OAc)_2$/dppb/$CO/H_2$

The carbonylative coupling of phenylacetylene and *p*-methylphenylacetylene with aniline was carried out with $Pd(OAc)_2$/dppb/$CO/H_2$ catalytic system. The isolated yields of the products are 98% and the ratio of *gem:trans* was found to be 74:26 and 70:30 respectively. The electron withdrawing nature of phenyl group enhances the addition of hydrogen to the terminal carbon atom of triple bond and [Pd] to the internal carbon atom, this was made possible due to the of planer less bulky nature of phenyl group.

The reason for the poor selectivity of *trans* isomer with phenylacetylene is mainly related to the electronic nature of the phenyl group [120]. A preliminary result using a palladium cationic complex, recently described by Inoue (Table 6, entry 6.7) [40] ($[Pd(dppb)(PhCN)_2](BF_4)_2$/$CO/H_2$) improved the selectivity of *trans* (21:79 *gem:trans*).

### 3.2.10 Reaction mechanism for trans-α,β-unsaturated ester derivatives

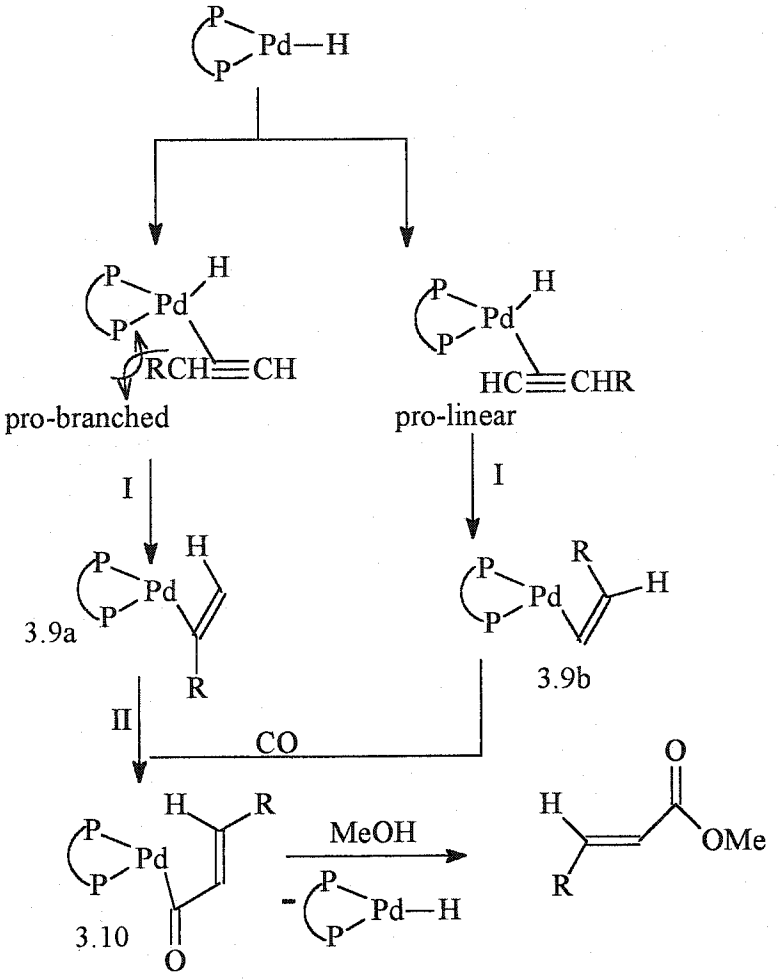
The proposed mechanisms for *trans-α,β*-unsaturated ester derivatives are few, due to the limited number of catalytic systems that afford *trans* isomers. Knifton [47] in 1977 proposed the initial η-alkyne complexation **(3.6)**, followed by the formation of vinylic species **(3.7)** through 1,2-hydride insertion, and the formation of acyl-Pd species *via* CO insertion **(3.8)**, and finally the alcoholysis to give the final product (Scheme 20).




L = $PPh_3$, $SnCl_3$, $Cl^-$, CO, or solvent.

Scheme 20

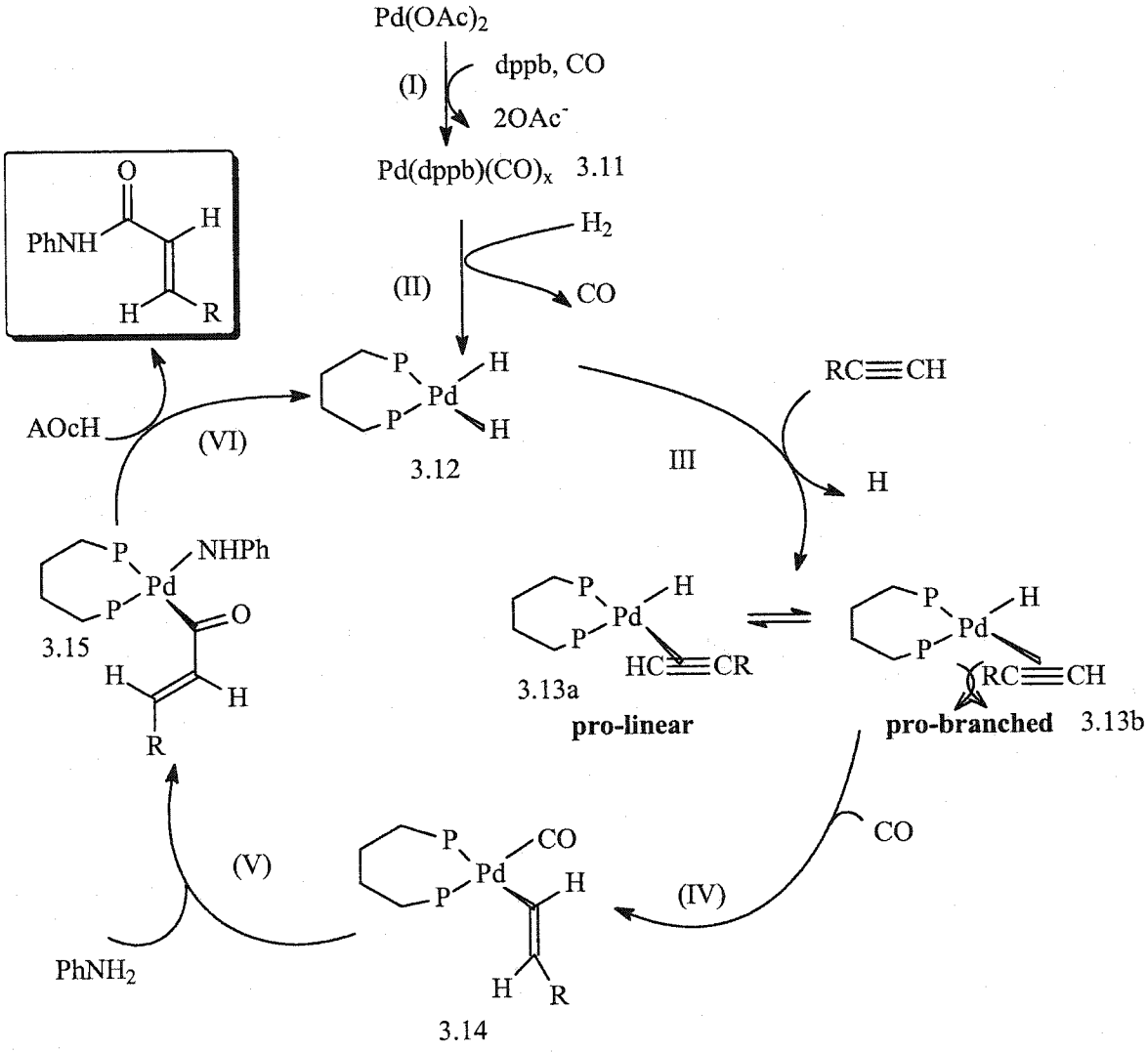
Recently, Inoue [40] proposed a similar mechanism (Scheme 21), which involves the following steps: I) insertion of the coordinated alkyne into Pd-H bond to give a (vinyl) palladium complex (**3.9a** or **3.9b**); II) CO insertion into Pd-C bond to afford an acylpalladium complex (**3.10**); III) methanolysis of the acyl complex to yield the *trans* ester and regenerate the hydride. The regiochemistry of the reaction is determined in step.




Scheme 21

### 3.2.11 Reaction mechanism proposed for $Pd(OAc)_2$/dppb/CO/$H_2$ systems

The analysis of the literature, coupled with the enhanced yield obtained with hydrogen (Figure 3.4), we tentatively proposed the metal hydride mechanism for the catalytic system that involves the following steps:




Scheme 22. Proposed mechanism for $Pd(OAc)_2$/dppb/CO/$H_2$ system

**Step I.** Palladium acetate, dppp and CO react to form $Pd(CO)_x(dppp)$ **(3.11)**, the value of x depend on CO pressure and this step has been well established in the literature [75].

**Step II.** Pd (0) formed in step I is known to be electron-rich [75] and basic [134] (pH 9.5), thus reacts with hydrogen to form Pd-H, the active catalytic species [135] **(3.12)** or on the alternatively the active species can be formed by the interaction between $[Pd(OAc)_2]$ and $H_2$ [136]. The former is more plausible due to the *in situ* formation of Pd(0) under CO atmosphere [96].

**Step III.** The alkyne, which is nucleophilic in nature, immediately coordinates to palladium center through π-coordination **(3.13a or 3.13b)**. The addition of Pd-H to the internal carbon of 1-alkyne would place the substituent R close to the bulky diphosphine ligand (pro-branched) intermediate **(3.13b)**. The interaction would further increase with the backbone rigidity and the bite angle of the ligand. In such circumstances, the pro-linear Pd intermediate **(3.13a)** rather than pro-branched **(3.3b)** may be more stable [40].

**Step IV.** The 1,2-addition hydride insertion to form σ-alkenyl ligand. Two types of coordination are possible when it rearranges from $\pi$ to σ-coordination (1,2-addition) depending on the electronic and steric nature of the palladium center. It depends also on the reaction conditions such as temperature, CO partial pressure. At high pressure of CO palladium dicarbonyl species may predominate leading to less steric hindrance resulting in more branched. The change in the electron density around the Pd metal center will lead to an increase in the linear isomer [75].

**Step V.** The formation of acyl-Pd species *via* CO insertion.

**Step VI.** The cleavage of palladium acyl intermediate forms the product and regenerates the active species. The most probable candidate for inducing such cleavage is the acetate anion [76].

## 3.3 Conclusion

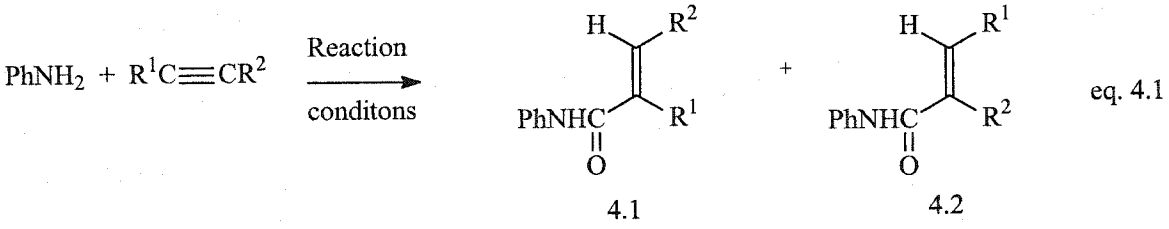
Various *trans*-$\alpha,\beta$-unsaturated amides have been synthesized by carbonylation coupling of terminal alkynes with aniline derivatives using $Pd(OAc)_2$/dppb/$CO/H_2$ catalytic system. The low rate of the reaction for $Pd(OAc)_2$/dppb/$CO/H_2$ compared to $Pd(OAc)_2$/dppp/$CO/H^+$ is related to the absence of the acid that enhances the rate of formation of Pd-H. In this system, both the steric and the electronic factors of the ligand and that of the substrate affect the regioselectivity of the reaction, however, the steric effect seems to be the dominant factor due to the less ionic catalytic system compared to $Pd(OAc)_2$/dppp/$CO/H^+$ system.

# CHAPTER 4

# TRANSITION METAL CATALYZED CARBONYLATIVE COUPLING OF INTERNAL ALKYNES WITH ANILINE DERIVATIVES INTO $\alpha,\beta$-DISUSBTITUTED UNSATURATED AMIDES

## 4.1 Introduction

The synthesis of $\alpha,\beta$-disubstituted unsaturated amides by direct carbonylative coupling of internal alkynes with aniline derivatives was achieved using $Pd(OAc)_2$/dppp/$CO/H_2$ (A) and $Pd(OAc)_2$/dppb/$CO/H^+$ (B) catalytic systems. The carbonylation of internal alkynes with $Pd(OAc)_2/PPh_3$ promoted with HI system failed to yield any carbonylated product [62]. A moderate yield of 50% $\alpha,\beta$-disubstituted unsaturated amide was obtained by reacting diphenylacetylene and diethylamine with stoichiometric amount of $NaHFe(CO)_4/I_2$ catalytic system [137].




4.1 4.2 eq. 4.1

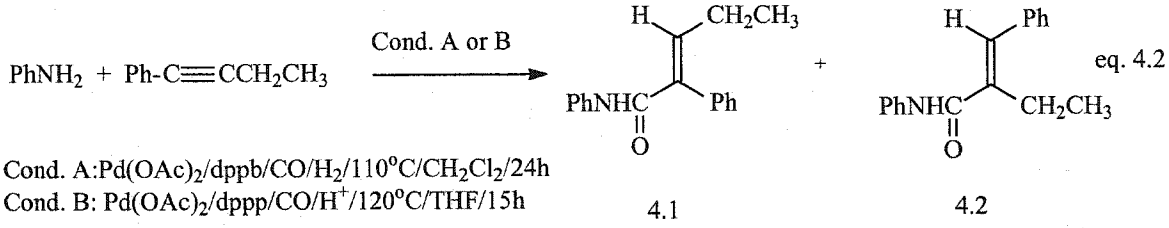
## 4.2 Results and discussion

Aniline and 1-phenyl-1-butyne were chosen as model substrates to study the effect of various parameters on the catalytic activity and the selectivity of the reaction. The effect of different phosphine ligands was studied with $Pd(OAc)_2$/dppb/$CO/H_2$ (A) in $CH_2Cl_2$ and $Pd(OAc)_2$/dppp/$CO/H^+$ (B) in THF.

Figure 4.1 shows the results of the effect of varying the type ligand on the yield and the selectivity of the reaction. *(E)-N*-2-Diphenyl penteneamide **(4.1)** when hydrogen is attached to a more sterically hindered carbon of the triple bond, and *(E)-N*-3-diphenyl 2-ethyl propeneamide **(4.2)** when hydrogen is added to less sterically hindered carbon. A moderate to low total yield (5% - 75%) was obtained when syngas with system A was used to give a mixture of **4.1** and **4.2** in good to moderate selectivity. It is worthy to mention that acceptable yields (75%, 58%) of products were obtained using dppb and $PPh_3$, respectively, whereas only 5% and 18% total yields of products were obtained under the syngas conditions with dppp and dppe used as ligands, respectively. Good selectivity in favor of the amide **4.1** (84%, 86%) was observed when dppe and $PPh_3$ were used as ligands.

On the other hand, when *p*-TsOH was used as an additive in place of $H_2$ gas, an increase in the total yields at shorter reaction time were observed (24h for $CO/H_2$ to 15h CO/*p*-TsOH). High total yields 86% and 95% were obtained using $Pd(OAc)_2$/CO/*p*-TsOH system when dppb and dppp were used as ligands, with products distribution of 55:45 and 60:40 in favor of **4.1** respectively. The differences of the catalytic activity of the two systems, $CO/H_2$ and CO/*p*-TsOH, are very clear from the results obtained by using dppp as a ligand; in both runs only 5% total yield was formed using $CO/H_2$ after 24h, whereas 95% total yield was achieved after 15h using CO/*p*-TsOH system with almost similar product distribution in favor of **4.1**. The catalysts, ligands, and solvents screening

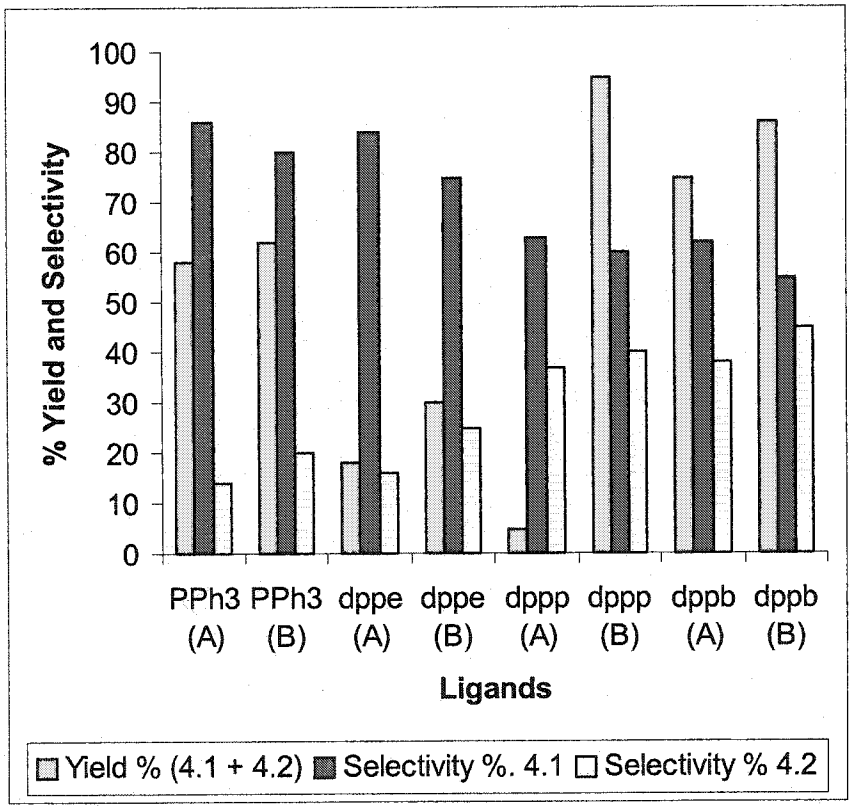
**Carbonylative coupling of internal alkynes with aniline catalyzed by $Pd(OAc)_2$/ligand/CO/$H_2$ (A) & $Pd(OAc)_2$/ligand/CO/$H^+$ (B); Effect of different ligands**




eq. 4.2

Cond. A:$Pd(OAc)_2$/dppb/CO/$H_2$/110°C/$CH_2Cl_2$/24h
Cond. B: $Pd(OAc)_2$/dppp/CO/$H^+$/120°C/THF/15h

4.1 4.2




General reaction conditions for catalyst system A: $Pd(OAc)_2$ (0.02 mmol), ligand (0.08 mmol), aniline & 1-phenyl-1-butyne (2.0 mmol), $CH_2Cl_2$ (10.0 ml), $H_2$ (300 psi), CO (300 psi), 110°C, 24h.
General conditions for catalytic system B: 0.12 mmol *p*-TsOH, 120°C, 100 psi CO, 2.0 mmol of various substrates, 0.04 mmol ligand, 0.02 mmol $Pd(OAc)_2$, THF (10ml), 15h.

**Figure 4.1**

indicated clearly that the catalytic system $Pd(OAc)_2$/dppp/CO/$H^+$ in THF gave the highest catalytic activity (Figure 4.1).

**4.2.1 Catalytic carbonylative coupling of internal alkynes with aniline derivatives**

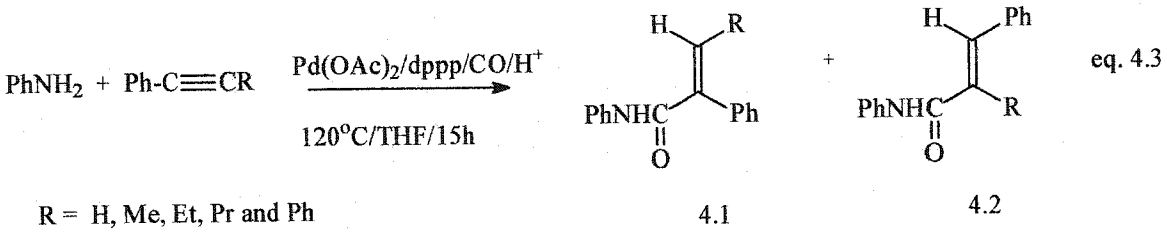
The reaction of aniline with different internal alkynes was performed with $Pd(OAc)_2$/dppp/CO/$H^+$ in THF for 15 h, the result as shown in Figure 4.2. When the substituent (R) is H, Me, Et, Pr and Ph, the selectivity for **4.1** were 96, 51, 60, 68 and 100, respectively. The yield decreased from phenylacetylene where (R = H) to 1-phenyl-1-propyne where (R = Me) and increases again when (R = Et) and 100% in diphenylacetylene.

The reason for the differences in yield and selectivity between phenylacetylene and 1-phenyl-1-propyne can be both steric and electronic. Since Me is an electron donating group it reduces the reactivity of the adjacent carbon and the tendency of [Pd] complex to attack this carbon.

The poor regioselectivity for the two isomers with 1-phenyl-1-propyne (ratio **4.1:4.2** = 51:49) could be rationalized in terms of similar sizes of the two substituents, i.e. Me and Ph on the two ends; consistent with this a large difference in the steric bulk of the two substituents wound be expected to improve the regioselectivity. Indeed, replacing Me with Et under the same conditions improved the regioselectivity [35,76] to 60:40 in favor of *(E)-N*-2-diphenyl penteneamide **(4.1)**, due to the fact that Et is bulkier than Me and also a stronger donating group. Similar increased was observed when R was propyl.

Similarly, when ethyl phenyl propiolate was carbonylated with a catalytic system B, the yield was 60% and a ratio of **4.1**: **4.2** of 33:66. It is well documented in literature that the addition of H-COOH to an acetylenic linkage, generally takes place in a *cis*-

**Carbonylative coupling of different internal alkynes with aniline catalyzed by $Pd(OAc)_2$/dppp/CO/$H^+$; Effect of substituent on yield and selectivity**

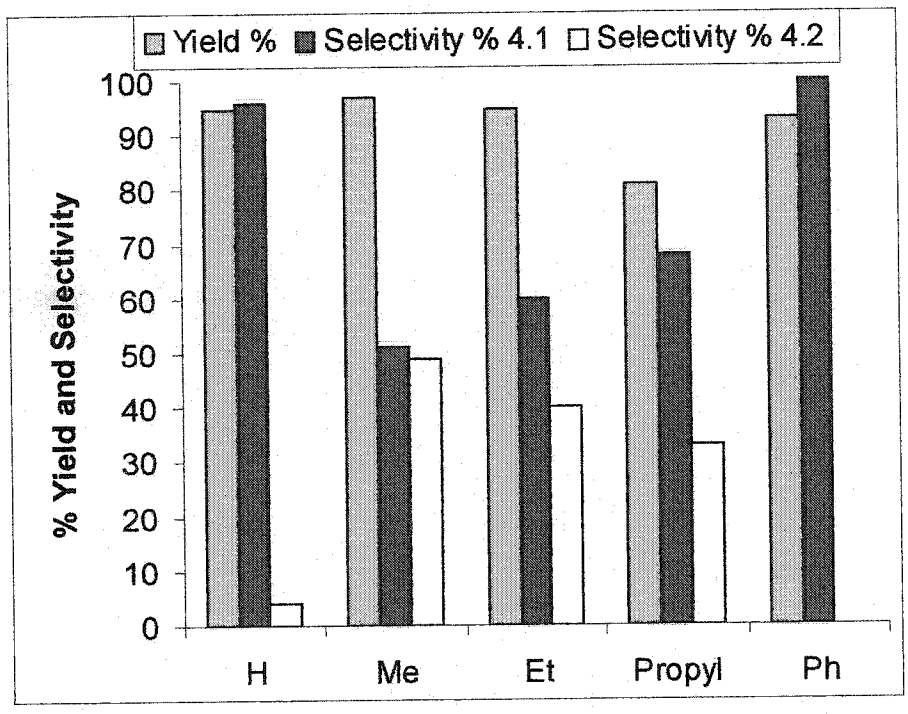



eq. 4.3

R = H, Me, Et, Pr and Ph

4.1

4.2

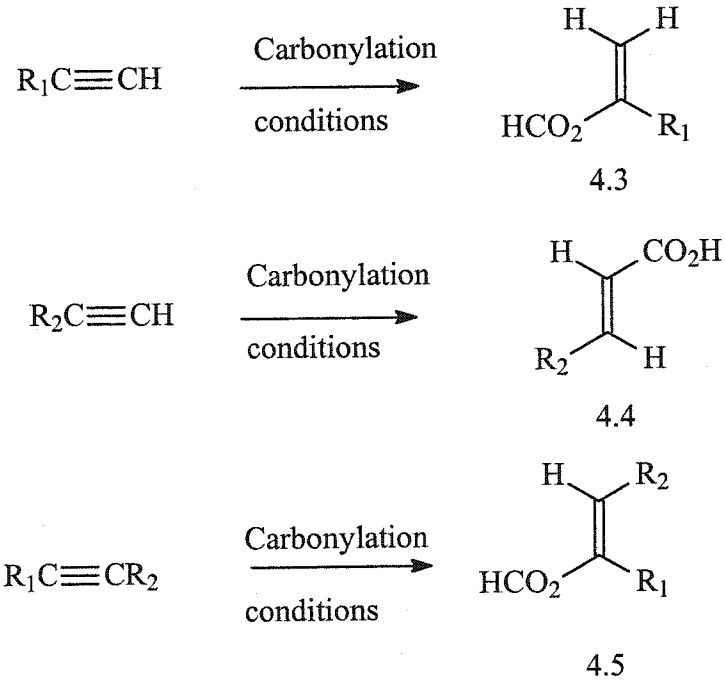



General reaction conditions: 0.12 mmol *p*-TsOH, 120°C, 100 psi CO, 2.0 mmol of various substrates, 0.04 mmol dppp, 0.02 mmol $Pd(OAc)_2$, THF (10ml), 15h, (a) Isolated yield (4.1 + 4.2) (b) Determined by GC and $^1H$ NMR

**Figure 4.2**

manner according to Markovnikov rule, although there are some exceptions [58,138,139]. The substituent of the alkyne plays an important role in determining the yield and which acetylenic carbon atom bonds to the carboxyl group [132,138,140]. For example, when $R_1$ is alkyl-, aryl-, $-CH_2OH$, $-CH_2CH_2OH$, or a $-CH_3COOCHR$, the COOH bond to the acetylenic carbon atom attached to $R_1$ **(4.3)** (Scheme 23).

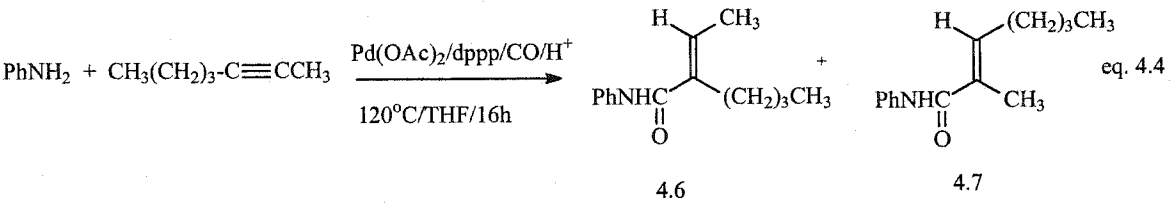
The reverse in regioselectivity was observed **(4.4)** with other types of substituent $R_2$ such as H, -CHROH, $-CR_2OH$, -COOH, $-COOCH_3$, $-COCH_3$, $-CH_2C(CH_3)OH$, with an internal alkyne that have both substituents from $R_1$, the reaction proceeds smoothly. If the substituents are from $R_1$ and $R_2$ the reaction is still reasonably fast with the COOH attached to acetylenic carbon containing $R_1$ **(4.5)**. If both substituents are from $R_2$, the reaction is not exothermic and gives only a low yield of unsaturated acid after prolonged heating. Of course, acetylene where R = H reacts smoothly [1,2].




Scheme 23

These results clearly explained the high yield when R group is both phenyl (diphenylacetylene). The lower yield and the reversal in regiochemistry in ethyl phenyl propiolate were caused by the presence of the group –COOEt that belongs to group $R_2$ and also electron withdrawing effect of COOEt.

Internal alkyl alkynes undergo carbonylative coupling with aniline derivatives. For example, 2-heptyne reacts with aniline using the catalytic system $Pd(OAc)_2$/dppb in $CH_2Cl_2$ at 130°C in the presence of syngas ($CO/H_2$) to give a mixture of *(E)-N*-phenyl-2-butyl-butaneamide (4.6) and *(E)-N*-phenyl-2-methyt-hepteneamide (4.7) in a ratio 33:67 and a total yield of 80%, (eq. 4.4). However, the catalytic system $Pd(OAc)_2$/dppp/*p*-TsOH in THF gave low yield of the products (20%) with a ratio of 4.6/4.7 = 30/70.




4.6 4.7 eq. 4.4

### 4.3.1 Conclusion

Carbonylative coupling of internal alkynes with aniline derivatives provides an efficient method for the synthesis of *N*-aryl-2,3-disubstitutesd acrylamides. The yields of the reaction are higher with $Pd(OAc)_2$/dppp/$CO/H^+$ (B) than with $Pd(OAc)_2$/dppb/$CO/H_2$ (A), whereas the selectivity is better in system A than in system B. Generally, the selectivity of the internal alkynes are lower than that of the terminal alkynes and a gradual improvement in selectivity was observed when there is a big difference in the effective bulkiness of the two substituents on the internal alkynes.

# CHAPTER 5

# EXPERAMENTAL SECTION

## 5.1 Instrumentation

$^{1}H$ NMR and $^{13}C$ NMR spectra were recorded on Jeol 500 lambda spectrometer. Chemical shifts were reported in ppm (δ) relative to tetramethyl silane (TMS) using $CDCl_3$. IR spectra were recorded on Perkin Elmer 16F PC FT-TR spectrometer and are reported in wave numbers ($cm^{-1}$). Gas chromatography analyses were recorded on HP 6890 chromatograph. Elemental analysis was done on Admirally Research Laboratory (ARL) atomic emission spectroscopy (AES) model ARL-3580. GC-MS was recorded on a VG 7070E mass analyzer.

Thin-layer chromatography (TLC) analyses were performed on silica gel Merk 60 F254 plates (250 μm layer thickness). A standard vacuum line equipped with two stage Edwards pump was used for handling air and moisture sensitive materials. Parr stainless autoclave fitted with glass liners were used for all high-pressure reactions. Reduced pressure rotovapor was used to remove the solvent after the reaction.

## 5.2 Chemicals and solvents

Chemical were purchased from commercial sources and were used without any purification unless were specified. All solvents were dried over molecular sieves prior to use.

## 5.3 General procedure with the catalytic system $Pd(OAc)_2$/dppp/CO/$H^+$

To a Parr autoclave fitted with a glass liner and stirring bar, was added $Pd(OAc)_2$ (0.02 mmol), dppp (0.04 mmol), terminal alkyne (2.0 mmol), aniline derivative (2.0 mmol), *p*-TsOH (0.12 mmol) and THF (10 ml). The autoclave was vented three times with CO and then pressurized with 100 psi CO. The mixture was stirred and heated for a required time. After cooling, the pressure was released, the reaction mixture filtered and the solvent was removed. Products were separated by recrystallization and or by preparative TLC (petroleum ether: acetone 10:1) and products identified by NMR, FT-IR, GC-MC, and elemental analysis.

## 5.4 General procedure with the catalytic system $Pd(OAc)_2$/dppb/CO/$H_2$

To a Parr autoclave fitted with a glass liner and stirring bar, was added $Pd(OAc)_2$ (0.02 mmol), dppb (0.08 mmol), terminal alkyne (2.0 mmol), aniline derivative (2.0 mmol), and $CH_2Cl_2$ (10 ml). The autoclave was vented three times with CO and then pressurized with 300 psi CO and 300 psi $H_2$. The mixture was stirred and heated for required time. After cooling, the pressure was released, the reaction mixture filtered, and the solvent was removed. Products were separated by recrystallization and/ or by preparative TLC (petroleum ether: acetone 10:1) and identified by NMR, FT-IR, GC-MC, and elemental analysis.

## 5.5 Synthesis of catalysts

**$Pd(OAc)_2$(dppp).** The literature procedure [97] was followed with little modification. 0.116 mmol of $Pd(OAc)_2$ was dissolved in toluene. The solution was filtered to remove Pd metal. A 0.235 mmol of dppp was dissolved separately in a minimum amount of toluene.

Dppp solution was then added slowly to a stirred solution of $Pd(OAc)_2$ over a period of five minutes. To the resulting solution, *n*-hexane at 60-80°C was then added to precipitate a white crystal of $Pd(OAc)_2$(dppp) complex. The complex was filtered and washed with *n*-hexane to yield 45% after drying under vacuum.

**$Pd(OTs)_2$(dppp).** The above complex, $Pd(OAc)_2$(dppp), was dissolved in toluene and two equivalent of *p*-TsOH was added with vigorous shaking in an Schlenk flask under nitrogen atmosphere. Immediate precipitation with *n*-hexane gave a white complex, which was allowed to settle down. The supernatant liquid was decanted and complex washed several times with n-hexane and finally with a little ether and dried in vacuum [97] to yield 60% of the complex.

**$Pd(OAc)_2$(dppb)**. The literature procedure [76] was followed with little modification. 0.116 mmol of $Pd(OAc)_2$ was dissolved in toluene. The solution was filtered to remove Pd metal. A 0.235 mmol of dppb was dissolved separately in a minimum amount of toluene. Dppb solution was then added slowly to a stirred solution of $Pd(OAc)_2$ over a period of five minutes. To the resulting solution, *n*-hexane at 60-80°C was then added to precipitate a yellowish white crystal of $Pd(OAc)_2$(dppp) complex. The complex was filtered and washed with *n*-hexane to yield 55% of complex after drying under vacuum.

**$Pd(dppb)Cl_2$** The literature procedure [135] was followed with no modification. 0.171g of $PdCl_2$ was dissolved in refluxing acetonitrile, then the hot solution was filtered to while still hot, and 0.426g of dppb (1:1 mole ratio with the metal) was added and stirred for an hour. After stirring, the volume was reduced; complex filtered off, recrystallized from dimethylformamide, and then dried in vacuum for 24 h. Yield 40 %.

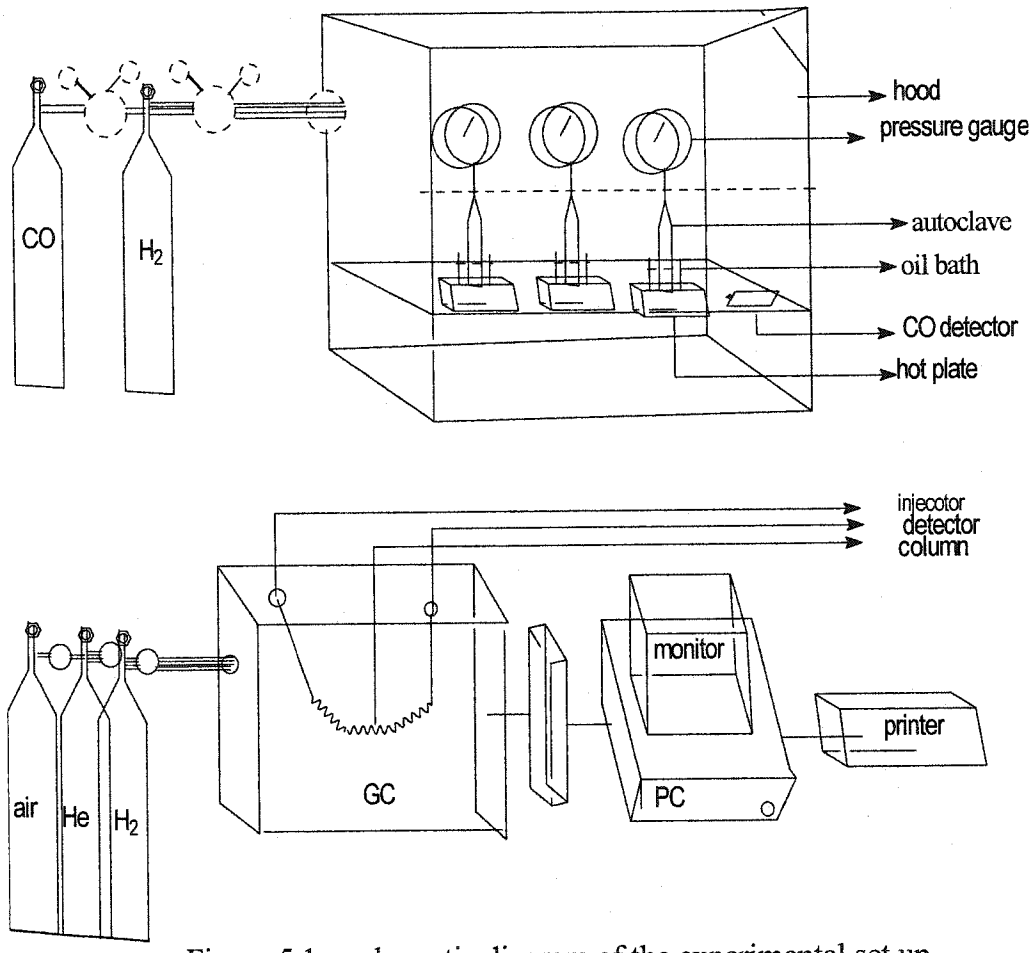
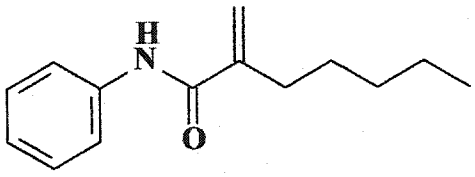



Figure 5.1 a schematic diagram of the experimental set up

**$[Pd(dppb)(PhCN)_2](BF_4)_2$.** The literature procedure [141,142] was followed with no modification. 0.001mol was dissolved in dichlorometane-benzonitrile (7:1 v/v 40 $cm^3$) and $AgBF_4$ (0.002 mol) dissolved in nitromethane (25 $cm^3$) added with stirring. After 3h the solution was filtered and reduced to small volume in vacuum. A yellow solid was precipitated by drop-wise addition of diethyl ether. The product was filtered off, washed with diethyl ether and dried under in vacuum at room temperature to yield 45 %.

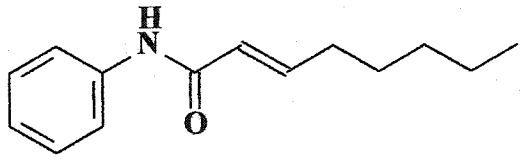
## 5.6 Spectra and analytical data for some of the synthesized unsaturated amides



**1. *β-4.3 N*-Phenyl 2- pentyl propeneamide**

**$^1$H NMR δ (ppm) $CDCl_3$:** 0.90 (t, 3H, J = 6.7, –C<u>H</u>$_3$), 1.31 (m, 4H, -(C<u>H</u>$_2$)$_2$CH$_3$), 1.59 (m, 2H, -C<u>H</u>$_2$-), 2.38 (t, 2H, J = 7.9, CC<u>H</u>$_2$-) 5.36 (s, 1H, - C<u>H</u>$_2$), 5.68 (s, 1H, =C<u>H</u>$_2$), 7.08-7.58(m, 5H, C$_6$<u>H</u>$_5$-), 7.74 (s, 1H, N<u>H</u>). **$^{13}$C NMR $\delta$ (ppm) $CDCl_3$:** 14.03, 22.46, 27.82, 31.46 32.42, 117.66, 120.05, 124.34, 128.97 (<u>C</u>$_6$H$_5$-), 137.92(=<u>C</u>H$_2$), 146.49 (<u>C</u>=CH$_2$) 167.28 (CO). **IR $\nu$ ($cm^{-1}$) KBr:** 3342 (sh, NH), 16.56 (sh, CO). M/z 217 ($M^+$), Anal. Calcd. For $C_{14}H_{19}NO$. C, 77.42; H, 8.76; N, 6.45; Found: C, 78.51; H, 9.43; N, 6.49.

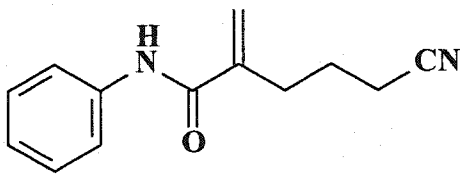
**2. *α-9.3 N*-Phenyl-2-octenamide**



**$^1$H NMR $\delta$ (ppm) $CDCl_3$:** 0.90 (t, 3H, J = 6.7, C<u>H</u>$_3$-), 1.31 (m, 4H, -C<u>H</u>$_2$CH$_3$), 1.71 (m, 4H, -(C<u>H</u>$_2$)$_2$- ), 2.12 (q, =CHC<u>H</u>$_2$), 5.91-5.94 (d, 1H, -CH=C<u>H</u>-CO, J = 15.25 Hz), 6.92-6.95 (m, 1H, -C<u>H</u>=CH-CO), 7.09-7.70 (m, 5H, C$_6$<u>H</u>$_5$- + 1H -N<u>H</u>). **$^{13}$C NMR $\delta$ (ppm) $CDCl_3$:** 13.81, 22.29, 22.38, 27.8, 31.19, 31.53, 31.99, 34.44, 121.48, 123.72, 129.00, 136.00, 146.75, 164.80 (CO). **IR neat $\upsilon$ ( $cm^{-1}$),** NH (br, 3270), 1666, CO (sh, 1667). M/z

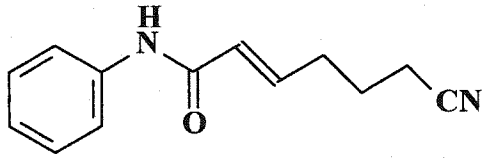
217 ($M^+$). Anal. Calcd. For $C_{14}H_{19}NO$. C, 77.42; H, 8.76; N, 6.45; Found: C, 78.01; H, 9.23; N, 6.47.

**3. β-4.1 *N*-Phenyl-3-propylnitriele –2-propeneamide**



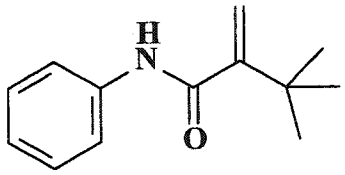

**$^1$H NMR δ (ppm) $CDCl_3$:** 1.18 (m, 2H, (-C<u>H</u>$_2$-), 2.37 (t, 2H, J = 8.05, -CC<u>H</u>$_2$CN), 2.54 (t, 2H, J = 7.15, (-CC<u>H</u>$_2$), 5.59 (s, 1H, =C<u>H</u>$_2$), 5.75 (s, 1H, =C<u>H</u>$_2$) 7.11 – 7.56 (m, 5H, $C_5$<u>H</u>$_5$-), 7.86(s, br, 1H, -N<u>H</u>). **$^{13}$C NMR δ, (ppm) $CDCl_3$:** 16.50, 23.86, 31.56, 119.2, 119.25, 119.46, 120.15, 124.49, 128.88 (<u>C</u>$_6$H$_5$-), 137.56 (=C<u>C</u>H$_2$), 144.08 (<u>C</u>=CH$_2$), 166.37 (CO). **IR ν ($cm^{-1}$) Neat:** 3311 (br, NH), 1683 (CO, br), 2218 (sh, CN) M/z 242 ($M^+$), Anal. Calcd. For $C_{12}H_{12}N_2O$. C, 72.00; H, 6.00; N, 14.00; Found: C, 86.72; H, 8.21; N, 14.92.

**4. α-9.3 *(E)-N*-phenyl-6-cyano-2-pentenamide**



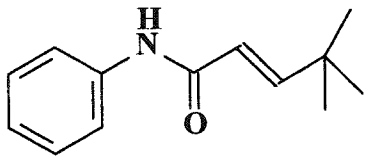

**$^1$H NMR δ (ppm) $CDCl_3$:** 1.73 (t, 2H, J = 7.08, -C<u>H</u>$_2$CN), 2.30 (m, 4H, -C<u>H</u>$_2$-), 6.05-6.08 (d, 1H, CO-C<u>H</u> = CH- J = 15.55 Hz), 6.83 (m, 1H, COCH =C<u>H</u>-), 7.08 – 7.61 (m, 5H, $C_6$<u>H</u>$_5$-), 8.36 (1H, -N<u>H</u>, br), **$^{13}$C NMR δ (ppm), $CDCl_3$:** 16.31, 23.66, 30.39, 119.19, 120.09, 124.20, 125.88, 128.75, 128.83 (<u>C</u>$_6$H$_5$-), 163.88 (CO). **IR Neat ν ($cm^{-1}$):** 3300 (NH, br), 2262 (CN, sh, med), 1683 (CO, sh). GC-MC M/z 214 ($M^+$). Anal. Calcd. For $C_{12}H_{12}N_2O$. C, 72.00; H, 6.00; N, 14.00; Found: C, 86.72; H, 8.21; N, 14.92.

**5. β-4.5 N-Phenyl-2-(2,2-dimethyl ethyl) propeneamide.**



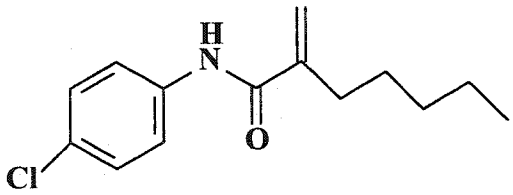
**$^1$H NMR δ (ppm) $CDCl_3$:** 1.12 (s, 9H, $C(C\underline{H}_3)_3$), 5.36 (d, 2H $=CH_2$, J = 25.05 Hz), 6.98-7.56 (m, 6H, $C_5\underline{H}_5$- & 1H, -N<u>H</u>). **$^{13}$C NMR δ (ppm) $CDCl_3$:** 29.32 $-C(\underline{C}H_3)_3$, 35.39 $\underline{C}(CH_3)_3$, 113.39, 119.85, 124.33, 128.99 ($C_{\underline{6}}H_5$-), 137.9 ($C\underline{H}_2$), 156.72 ($-\underline{C}=CH_2$), 168.18 (CO). **IR ν ($cm^{-1}$) KBr:** 3244 (NH, br), 1656 (CO, sh). M/z 203 ($M^+$), Anal. Calcd. For $C_{13}H_{17}NO$. C, 76.847; H, 8.37; N, 6.90; Found: C, 76.91; H, 8.15; N, 6.79.

**6. α-9.5 *N*-Phenyl – 4,4-dimethyl-2-butenamide**



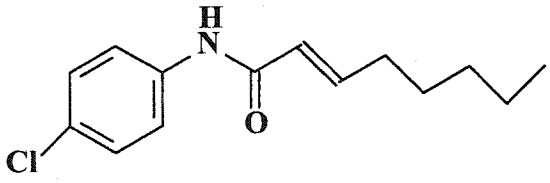
**$^1$H NMR, δ (ppm) $CDCl_3$:** 1.11 (s, 9H, $C(C\underline{H}_3)_3$), 5.81-5.84 (d, 1H, -CH=C<u>H</u>-CO J = 15.25 Hz), 6.98- 7.01 (d, 1H, -C<u>H</u>=CH-CO., J = 15.25 Hz), 7.09-7.56 (m, 6H, $C_6\underline{H}_5$- + 1H N<u>H</u>) **$^{13}$C NMR δ (ppm), $CDCl_3$:** 28.83 $-C(\underline{C}H_3)_3$, 33.67 $-\underline{C}(CH_3)_3$, 119.85, 124.21, 129.00 ($\underline{C}_6H_5$-), 156.37, 164.54 (CO), ***IR*** **υ ($cm^{-1}$), KBr:** 3238 (br, NH), 1668 (sh, CO). M/z 203 ($M^+$), Anal. Calcd. For $C_{13}H_{17}NO$. C, 76.847; H, 8.37; N, 6.90; Found: C, 76.91; H, 8.15; N, 6.79.

**7. β-4.8 *N*-(4-Chlorophenyl)-2-pentyl propeneamide**



**$^1$H NMR δ (ppm) $CDCl_3$:** 0.89 (t, 3H, J = 6.6, -C<u>H</u>$_3$), 1.33 (m, 4H, -(C<u>H</u>$_2$)CH$_3$), 1.50 (m, 2H, -C<u>H</u>$_2$-), 2.38 (t, 2H, J = 7.85, -CC<u>H</u>$_2$-), 5.40 (s, 1H, (=C<u>H</u>$_2$)), 5.70 (s, 1H, =C<u>H</u>$_2$), 7.26-7.53 (m, 4H, $C_6$<u>H</u>$_4$-), 7.58 (s, br, -N<u>H</u>). **$^{13}$C NMR δ (ppm) $CDCl_3$:** 13.97, 22.41, 27.80, 31.42, 32.33, 117.91, 121.16, 128.99, 129.31, 136.41, 146.29, 167.01 (<u>C</u>O). **IR (υ cm$^{-1}$) KBr:** 3328 (sh, NH), 1660 (sh, CO), 822 (s, *p*-subst.). M/z 251 ($M^+$). Anal. Calcd. For $C_{14}H_{18}NOCl$. C, 66.80; H, 7.16; N, 5.57; Found: C, 67.13; H, 7.61; N, 5.43.

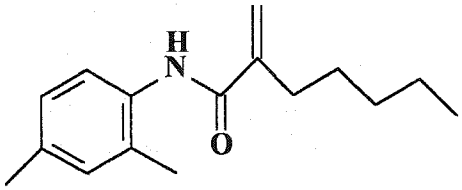
**8. α-9.8 *N*-(4-chlorophenyl) -2-octeneamide**



**$^1$H NMR (δ ppm) $CDCl_3$:** 0.87(t, 3H, J = 16.95, C<u>H</u>$_3$-), 1.26 (m, 4H, -(C<u>H</u>$_2$)$_2$CH$_3$), 1.37 (m, 2H, -C<u>H</u>$_2$- ), 2.12 (m, CH=CHCO), 6.01-6.04 (d, 1H, -CH=C<u>H</u>-CO, J = 15.25 Hz), 6.92-6.95 (m, 1H, -C<u>H</u>=CHCO), 6.92-8.64 (m, 5H, $C_6$<u>H</u>$_4$- + 1H, N<u>H</u>). **$^{13}$C NMR δ (ppm) $CDCl_3$:** 13.81, 22.29, 22.38, 27.8, 31.19, 31.53, 31.99, 34.44, 121.48, 123.72, 129.00, 136.00, 146.75, 164.80 (CO). **IR υ (cm$^{-1}$) KBr:** 3300 (br, NH), 1677 (sh, CO), 838 (s, *p*-

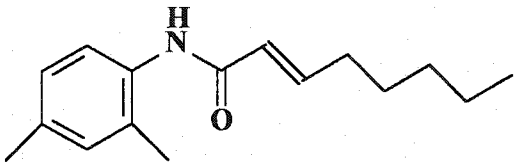
subst.). M/z 251, ($M^+$). Anal. Calcd. For $C_{14}H_{18}NOCl$. C, 66.80; H, 7.16; N, 5.57; Found: C, 67.86; H, 7.70; N, 5.51.

**9. β-4.13 *N*-(2,4-dimethylphenyl)-2-pentyl propeneamide**



**$^1$H NMR (δ ppm) $CDCl_3$**: 0.90 (t, 3H, J = 7.35, –C<u>H</u>$_3$), 1.34 (M, 4H, -(C<u>H</u>$_2$)$_2$), 1.51 (m, 2H, -C<u>H</u>$_2$-), 2.23 (s, 3H, Ph-C<u>H</u>$_3$), 2.29 (s, 3H, Ph-C<u>H</u>$_3$), 2.40 (t, 2H, J = 7.55, (C-C<u>H</u>$_2$)), 5.34 (s, 1H, (=C<u>H</u>$_2$)), 5.71 (s, 1H, (=C<u>H</u>$_2$)), 7.00-7.70 (m, 4H, $C_6$<u>H</u>$_3$ + N<u>H</u>). **$^{13}$C NMR δ (ppm) $CDCl_3$:** 13.39, 17.66, 20.83, 22.43, 27.83, 31.43, 32.52, 117.46, 123.13, 127.29, 129.13 ($C_6$<u>H</u>$_3$), 131.07, 132.97, (Ph-<u>C</u>H$_3$), 134.87, (C=<u>C</u>H$_2$), 146.53, <u>C</u>=CH$_2$), 167.00 (CO). **IR ν (cm$^{-1}$), Neat:** 3282 (NH, br), 1660 (sh, CO). M/z 251 ($M^+$). Anal. Calcd. For $C_{16}H_{23}NO$. C, 78.34; H, 9.34; N, 5.71; Found: C, 79.13; H, 9.96; N, 5.76…

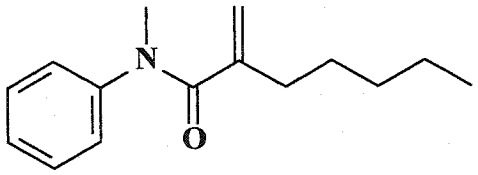
**10. α-9.13 *N*-(2,4-dimethylphenyl)-2-octeneamide**



**$^1$H NMR δ (ppm) $CDCl_3$**, 0.89 (t, 3H, J = 9.5, –C<u>H</u>$_3$), 1.30 (m, 4H, -(C<u>H</u>$_2$)$_3$), 1.52 (m, 2H, -C<u>H</u>$_2$-), 2.23 (s, 3H, Ph-C<u>H</u>$_3$), 2.29 (s, 3H, Ph-C<u>H</u>$_3$), 5.95-5.98 (d, 1H, -CO C<u>H</u>=CH, J = 15.25 HZ), 6.95-7.26 (m, 4H, -C<u>H</u>=CHCO + $C_6$<u>H</u>$_3$), 7.71 (s, br, N<u>H</u>)). **$^{13}$C NMR δ (ppm) $CDCl_3$**: 13.96, 17.74, 20.86, 22.43, 27.89, 31.35, 32.10, 123.27, 127.28, <u>C</u>$_6$H$_3$),

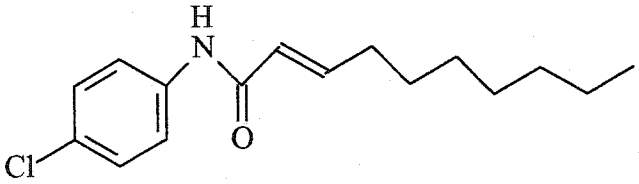
131.09, 133.09, (Ph-$\underline{C}H_3$), 146.22, (-$\underline{C}H$=CH-CO-), 154.62, -CH=C$\underline{H}$CO-), 164.56 (CO). **IR ν ($cm^{-1}$), KBr**: 3270 (br, NH), 1666 (CO, sh). M/z 251 ($M^+$). Anal. Calcd. For $C_{16}H_{23}NO$. C, 78.34; H, 9.34; N, 5.71; Found: C, 79.13; H, 9.96; N, 5.76.

**11. β-4.18 *N,N*-Methyl phenyl-2-pentylpropeneamide**



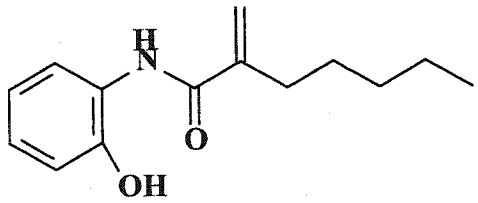
**$^1$H NMR (δ ppm), $CDCl_3$:** 0.86 (t, 3H, J = 7.3, -$CH_3$), 1.17-1.40 (m, 6H –$CH_2$-), 2.05 (t, 3H, J = 7.95, -$CCH_2$-), 3.35 (s, 3H, N-$CH_3$), 5.03 (s, 2H, =$CH_2$), 7.13-7.35 (m, 5H, $C_5H_5$-). **$^{13}$C NMR (δ ppm), $CDCl_3$:** 13.97, 22.41, 27.14, 31.37, 33.67, 37.79, 117.97, 126.76, 126.84, 129.12, 144.49, 145.36, 171.87 (CO). **IR υ ($cm^{-1}$), neat:** 1640 (CO).

**12. α-9.9 *N*-(4-chlorophenyl) -2-deceneamide**



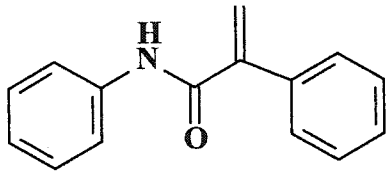
**$^1$H NMR (δ ppm) $CDCl_3$:** 0.87(t, 3H, J = 16.95, $C\underline{H}_3$-), 1.26 (m, 8H, -($C\underline{H}_2$)$_2CH_3$), 1.40 (m, 2H, -$C\underline{H}_2$- ), 2.15 (m, C$\underline{H}$=CHCO), 5.97-6.00 (d, 1H, -CH=C$\underline{H}$-CO, J 15.00 Hz), 6.92-6.95 (m, 1H, -C$\underline{H}$=CHCO), 6.92-8.64 (m, 5H, $C_6\underline{H}_4$- + 1H, N$\underline{H}$). **$^{13}$C NMR δ (ppm) $CDCl_3$:** 13.97, 22.53, 22.38, 28.16, 28.28, 29.08, 29.22, 32.21, 121.38, 123.67, 129.07, 136.73, 146.91, 164.63 (CO). **IR υ ($cm^{-1}$) KBr:** 3300 (br, NH), 1677 (sh, CO), 838 (s, *p*-subst.). M/z 279, ($M^+$).

**13. β-4.23 *N*(-2-hydroxylPhenyl)- 2- pentylproeneamide**



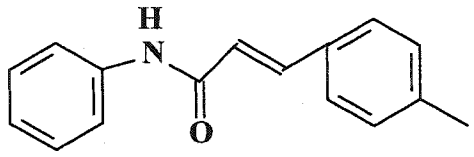
**$^1$H NMR δ (ppm) $CDCl_3$:** 0.91 (t, 3H, J 6.7, $-C\underline{H}_3$), 1.35 (m, 4H, $-(C\underline{H}_2)_2CH_3$), 1.54 (m, 2H, $-C\underline{H}_2-$), 2.41 (t, 2H, J 7.1, $CC\underline{H}_2-$) 5.49 (s, 1H, - $C\underline{H}_2$), 5.85 (s, 1H, $=C\underline{H}_2$), 6.89-7.26 (m, 5H, $C_6\underline{H}_5-$), 7.78 (s, 1H, N<u>H</u>). **$^{13}$C NMR δ (ppm) $CDCl_3$:** 13.95, 22.44, 27.76, 31.39, 32.37, 119.84, 119.89, 125.46, 127.69 ($\underline{C}_6H_5-$), 144.65 ($=\underline{C}H_2$), 148.91 ($\underline{C}=CH_2$) 168.22 (CO). **IR ν (cm$^{-1}$), KBr:** 3254 (br, NH and OH), 1694 (sh, CO).

**14. β-5.1 *N*,2-Diphenyl propeneamide**



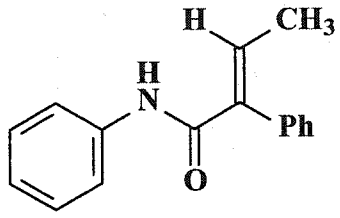
**$^1$H NMR δ (ppm), $CDCl_3$** 5.72 (s, 1H, $=CH_2$), 6.29 (s, 1H, $=CH_2$), 7.10-7.52 (m, 11H, 2Ph and NH); **$^{13}$C NMR δ (ppm) $CDCl_3$** 119.93, 123.36, 128.87, 129.02, 136.67, 137.65, 145.11, 165.20 (CO). **IR ν (cm$^{-1}$), KBr:** 3230 (NH), 1652 (sh, CO), GC-MC M/z 223 ($M^+$). Anal. Calcd. For $C_{15}H_{13}NO$. C, 80.69; H, 5.87; N, 6.27; Found: C, 80.75; H, 6.08; N, 6.34.

**15. α-5.2 *N*-Phenyl-3-*p*-tolyl propeneamide**



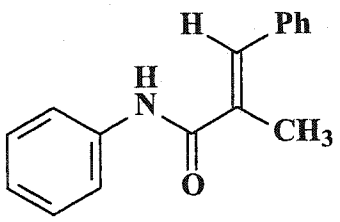
**$^1$H NMR δ (ppm), $CD_3Cl$:** 2.36 (s, 3H, $CH_3$), 6.53 (d, 1H, J 15.5 Hz, COCH=C<u>H</u>), 7.10-7.62 (m, 10H, arom. and NH), 7.72 (d, 1H, J 15.5Hz, COC<u>H</u>=CH-tolyl); **$^{13}$C NMR δ (ppm), $CDCl_3$:** 21.45, 119.98, 124.40, 127.96, 129.06, 129.61, 131.87, 138.10, 140.32, 142.32, 164.48; **IR υ ($cm^{-1}$), neat:** 1656 (CO), 3286 (NH); GC-MS, M/z 237 ($M^+$). Anal. Calcd. $C_{16}H_{15}NO$: C, 80.98; H, 6.37, N, 5.9. Found C, 79.95; H, 6.37, N, 5.85.

**16. $C_1$-10.1 *N*-Phenyl-2-phenyl buteneamide**



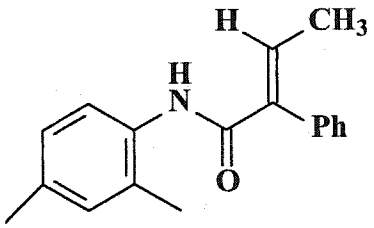
**$^1$H NMR δ (ppm), $CDCl_3$:** 1.71 (d, 3H, J 7.05) 7.04-7.51 (m, 12H, 2Ph + NH + olefinic proton]); **$^{13}$C NMR δ (ppm), $CDCl_3$:** 15.36, 119.90, 124.31, 128.47, 128.90, 129.24, 129.98, 135.13, 137.04, 137.65, 137.84, 164.64; **IR υ ($cm^{-1}$), neat:** 1658 (CO), 3238 (NH); GC-MS: M/z 237 ($M^+$), 160, 145, 117, 91, 77.

**17. $C_2$-10.1 *N*-Phenyl-2-methyl-3-phenyl propeneamide**



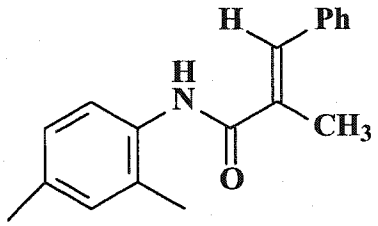

**$^1$H NMR δ (ppm), $CD_3Cl$:** 2.21 (d, 3H, J 1.0) 7.26-7.57 (m, 12H, 2Ph + NH + olefinic H); **$^{13}$C NMR δ (ppm), $CDCl_3$:** 14.43, 120.03, 124.37, 128.17, 129.85, 131.42, 135.90, 137.36, 139.47, 168.50; GC-MS: M/z 237 ($M^+$), 222, 145, 117, 102, 91, 77. IR **υ ($cm^{-1}$), neat:** 1664 (CO), 3228 (NH).

**18. $C_1$-10.2 *N*-(2,4-dimethylphenyl)-2-phenyl buteneamide**



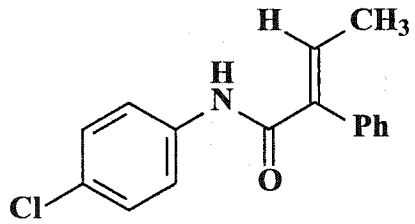

**$^1$H NMR δ (ppm), $CDCl_3$:** 1.72 (d, 3H, J 7.0) 1.81 (s, 3H), 2.24 (s, 3H), 6.89-7.88 (m, 10H, 8H arom. + NH + 1H olefinic); **$^{13}$C NMR δ (ppm), $CDCl_3$:** 15.30, 17.09, 20.82, 121.84, 127.29, 128.41, 129.18, 129.96, 130.91, 133.44, 134.27, 135.53, 137.10, 164.44; **IR υ ($cm^{-1}$), neat:** 1668 (CO), 3236 (NH). GC-MS: M/z 265 ($M^+$), 250, 145, 117, 91.

**19. $C_2$-10.2 *N*-(2,4-dimethyl phenyl)phenyl-2-methylpropeneamide**



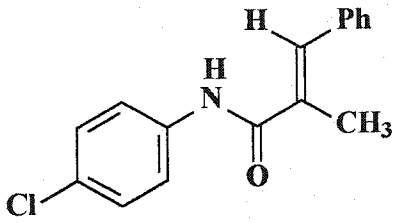

**$^1$H NMR δ (ppm), $CDCl_3$:** 2.22 (d, 3H, J 1.50) 2.27 (s, 3H), 2.31 (s, 3H), 7.03-7.73 (10H, 8H arom. + NH + 1H olefinic); **$^{13}$C NMR δ (ppm) $CDCl_3$:** 14.50, 17.78, 20.90, 123.31, 127.38, 128.01, 128.41, 129.40, 131.16, 132.70, 133.18, 134.38, 134.97, 135.95, 167.78; **IR υ ($cm^{-1}$), neat:** 1658 (CO), 3241 (NH); GC-MS: M/z 265 ($M^+$), 250, 145, 121, 117, 115, 106, 91, 77, 65.

**20. $C_1$-10.3 *N*-(4-chlorophenyl)-2-phenylbuteneamide**



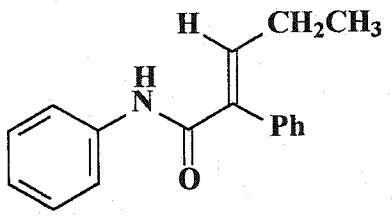

**$^1$ H NMR δ (ppm), $CDCl_3$:** 1.71 (d, 3H, C<u>H</u>$_3$, J 7.30 Hz), 7.21-7.59 (m, 10H, 9H arom. + 1H olefinic), 8.02 (s, 1H, NH); **$^{13}$C NMR δ (ppm), $CDCl_3$**: 15.26, 121.13, 127.40, 128.48, 129.28, 129.79, 134.44, 136.26, 164.69; GC-MS: 271, **IR υ ($cm^{-1}$), KBr:** 1662 (CO), 3236 (NH); GC-MS: M/z 271 ($M^+$), 145, 117, 91.

**21. $C_2$-10.3 *N*-(4-chlorophenyl)phenyl-2-methylpropeneamide**



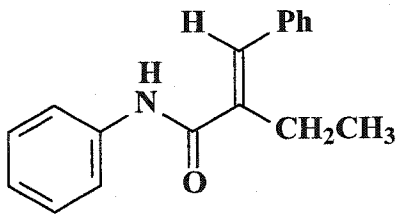

**$^1$H NMR δ (ppm), $CDCl_3$:** 2.18 (d, 3H, $CH_3$, J = 1.20 Hz), 7.19-7.56 (m, 10H, 9 arom. + 1H olefinic), 7.65 (s, 1H, NH); **$^{13}$C NMR δ (ppm), $CDCl_3$:** 14.44, 121.38, 128.19, 128.45, 129.04, 129.36, 132.55, 134.68, 135.65, 136.57, 167.78; **IR υ ($cm^{-1}$), KBr:** 658 (CO), 3242 (NH); GC-MS: M/z 271, 273 ($M^+$), 145, 117, 115, 91.

**22. $C_1$-10.1 *N*-Phenyl-2-phenyl penteneamide**



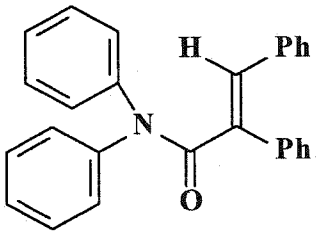

**$^1$H NMR δ (ppm), $CDCl_3$:** 1.02 (t, 3H, $C\underline{H}_3$, J = 7.65 Hz), 2.03 (q, 2H, $C\underline{H}_2$, J = 7.60 Hz); 7.05-7.49 (m, 12H, 10H arom. + 1H N$\underline{H}$ + 1$\underline{H}$ olefinic); **$^{13}$C NMR δ (ppm), $CDCl_3$:** 13.41, 22.90, 119.87, 124.29, 128.45, 128.89, 129.19, 129.88, 135.36, 135.55, 137.89, 144.12, 164.72; **IR υ ($cm^{-1}$), KBr:** 1652 (CO), 3230 (NH); GC-MS: M/z 251 ($M^+$), 222, 159, 132, 131, 116, 91, 77, 65.

**23. $C_2$-10.1 *N*-Phenyl-2-ethyl-3-phenyl propeneamide**



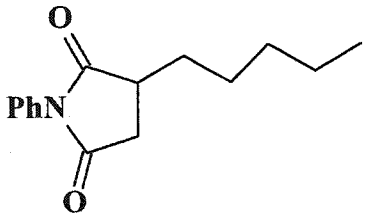

**$^1$H NMR δ (ppm), $CDCl_3$:** 1.21 (t, 3H, C<u>H</u>$_3$, J = 7.30 Hz), 2.66 (q, 2H, C<u>H</u>$_2$, J = 7.66 Hz); 7.12-7.62 (m, 12H, 10H arom. + 1H N<u>H</u> + 1<u>H</u> olefinic); **$^{13}$C NMR δ (ppm), $CDCl_3$:** 13.49, 21.35, 119.98, 124.40, 128.54, 128.92, 129.10, 132.56, 135.36, 143.25, 167.84; **IR υ ($cm^{-1}$), KBr:** 1652 (CO), 3230 (NH); GC-MS: M/z 251 ($M^+$), 222, 159, 132, 131, 116, 91, 77, 65.

**24. C-10.7 *N*-diphenyl-2,3-diphenylpropeneamide**




**$^1$H NMR δ (ppm), $CDCl_3$:** 7.05-7.56 (m, 21H, 20 aromatic + 1H olefinic); **$^{13}$C NMR δ (ppm), $CDCl_3$:** 121.69, 127.42, 128.68, 129.82, 134.86, 137.42, 143.12, 172.46; **IR ν ($cm^{-1}$), (neat):** 1662 (CO); GC-MS: M/z 375 ($M^+$).

**25. 2.3 *N*-phenyl-$\alpha$-butylsuccinimide**




**$^1$H NMR (ppm) $CDCl_3$:** 0.90 (t, 3H, J = 6.7, –C<u>H</u>$_3$), 1.31 (m, 4H, -(C<u>H</u>$_2$)$_2$CH$_3$), 1.59 (m, 2H, -C<u>H</u>$_2$-), 2.38 (t, 2H, J = 7.9, CC<u>H</u>$_2$-) 2.47 (d, -CHC<u>H</u>$_2$), 2.50 (d, -CHC<u>H</u>$_2$), 2.85-2.95 (m, -C<u>H</u>CH$_2$), 7.08-7.58 (m, 5H, C$_6$<u>H</u>$_5$-).

# CHAPTER 6

# CONCLUSION AND RECOMMENDATION

## 6.1 Conclusions

The results of the investigation indicate the following:

1. Excellent control of regioselectivity has been achieved in the catalytic synthesis of *gem* and *trans*-$\alpha,\beta$-unsaturated amide under mild reaction conditions.
2. The best conditions for the synthesis of *gem* isomers are $Pd(OAc)_2$/dppp/CO/*p*-TsOH in THF at 120°C where as that of *trans* are $Pd(OAc)_2$/dppb/CO/$H_2$ in $CH_2Cl_2$ at 110°C.
3. The regioselectivity of the reaction is controlled by both steric and electronic effect of the catalytic intermediate and substrate, under *trans* conditions steric effect is the major factor whereas under *gem* conditions the electronic is the major factor.
4. Enhancement of reaction by hydrogen and acids is an indication that both catalytic systems go through Pd-H mechanism.
5. *Gem* reactions are faster than *trans* reactions probably due to the presence of traces of water in the acid, which increases the rate of formation of Pd-H.
6. The poor selectivity for *trans* isomers in carbonylation of phenylacetylene with aniline derivatives is mainly attributed to the electronic effect of the phenyl group.
7. Carbonylative coupling of terminal alkynes with aniline derivatives is faster and more selective than the carbonylative coupling of internal alkynes.

8. The selectivity in carbonylative coupling of the internal alkynes with aniline derivates increases with the increase of the effective bulkiness of the substituents.
9. The *gem* catalytic systems easily get deactivated probably due to its quantization.
10. The synthesis of new unsaturated amides has been achieved.

## 6.2 Recommendations

1. Further investigation is needed to improve the yield and the selectivity of cyclic substituted imides.
2. To investigate further the improvement of the selectivity toward *trans* isomers in the carbonylation of aromatic alkynes.
3. To investigate the carbonylation of functionalized alkynes with aniline derivatives.
4. To investigate the carbonylation of dialkynes with aniline derivatives, diamines with alkynes and dialkynes with the diamines.
5. To investigate the possibility of carbonylative coupling alkynes with primary and secondary amines.

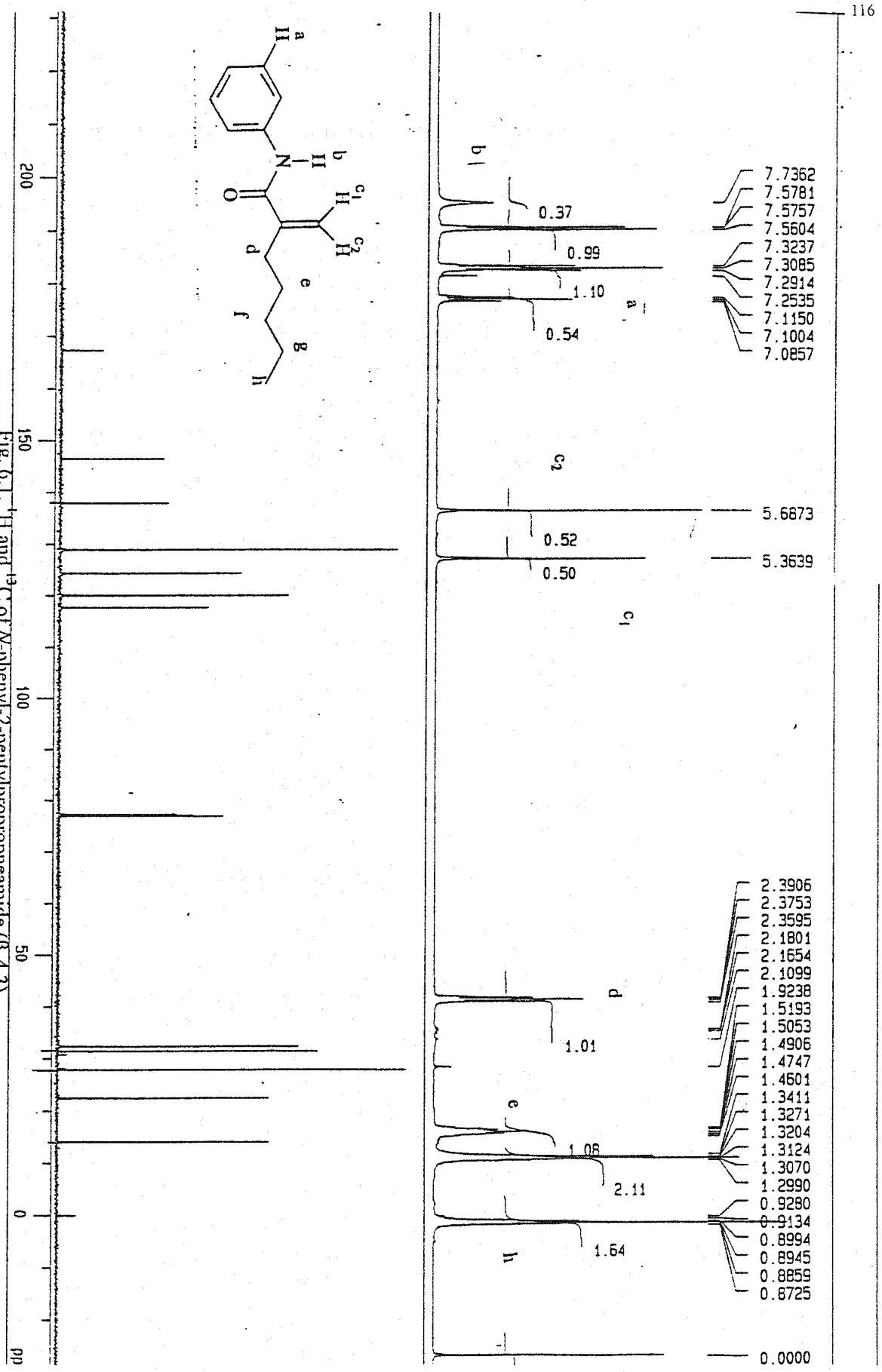



Fig. 6.1. $^{1}H$ and $^{13}C$ of *N*-phenyl-2-pentylpropropneamide (β-4.3)

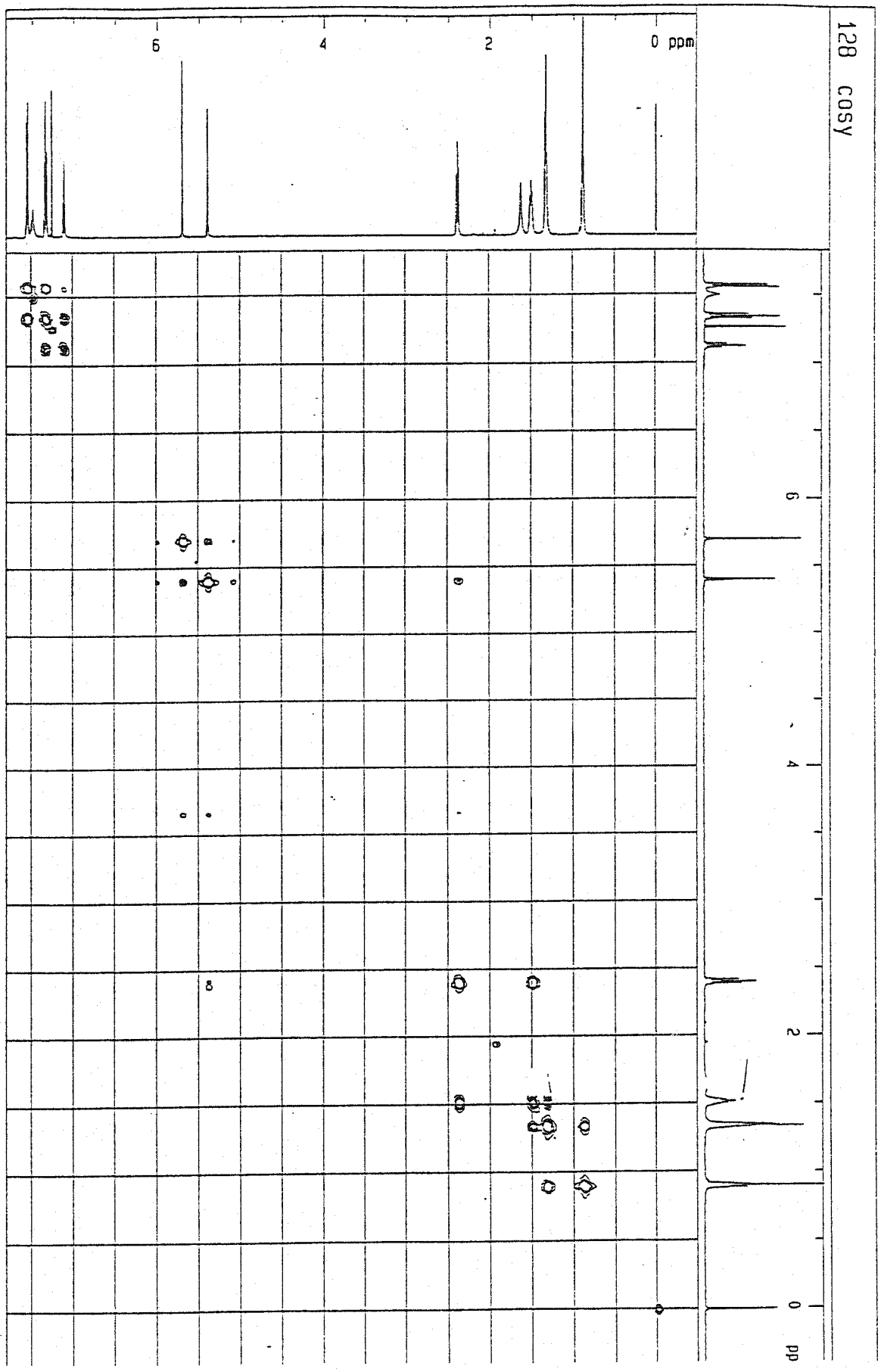



Fig. 6.2. cosy of *N*-phenyl-2-pentylpropropneamide (β-4.3)

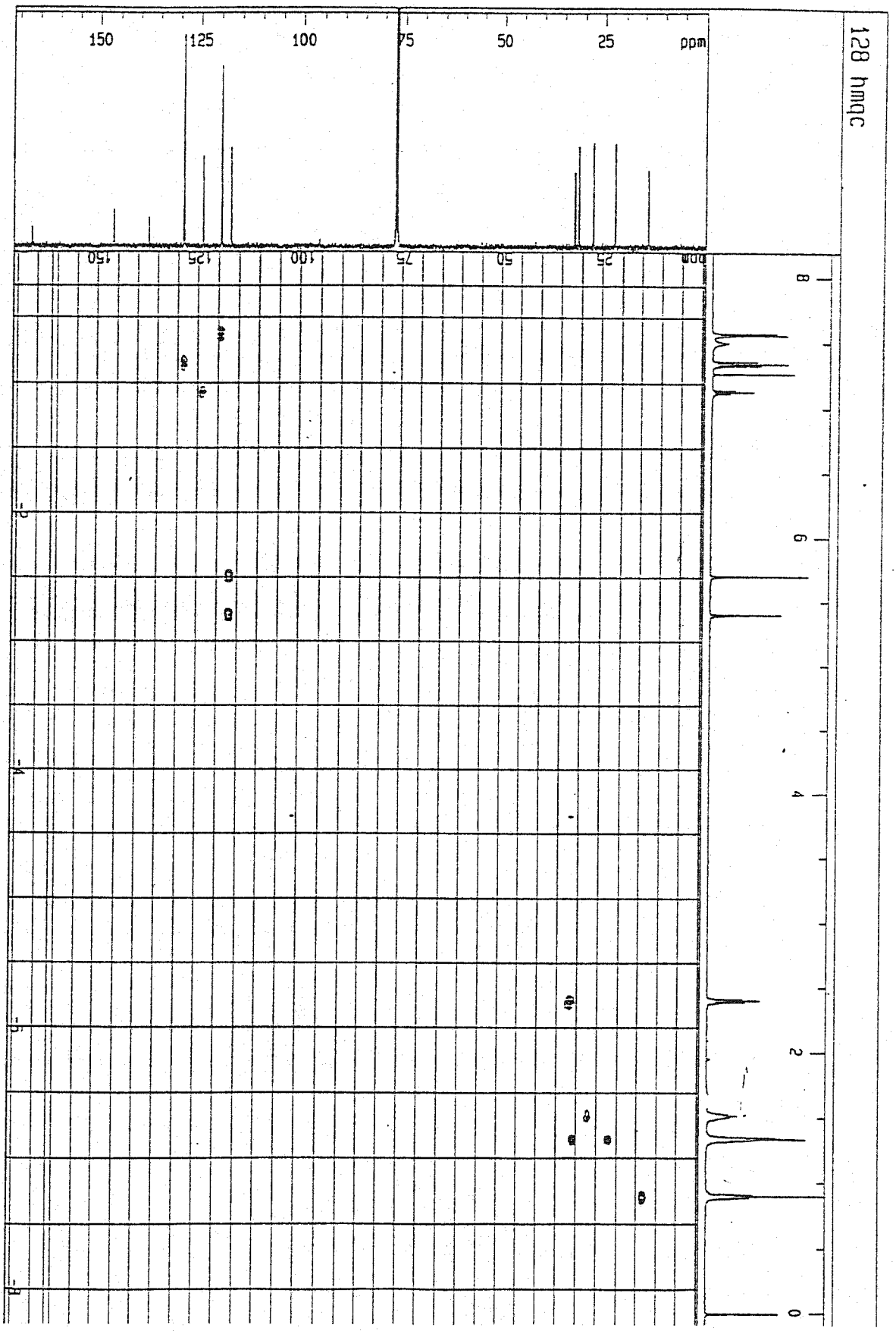



Fig. 6.3. hmqc of *N*-phenyl-2-pentylpropropneamide (β-4.3)

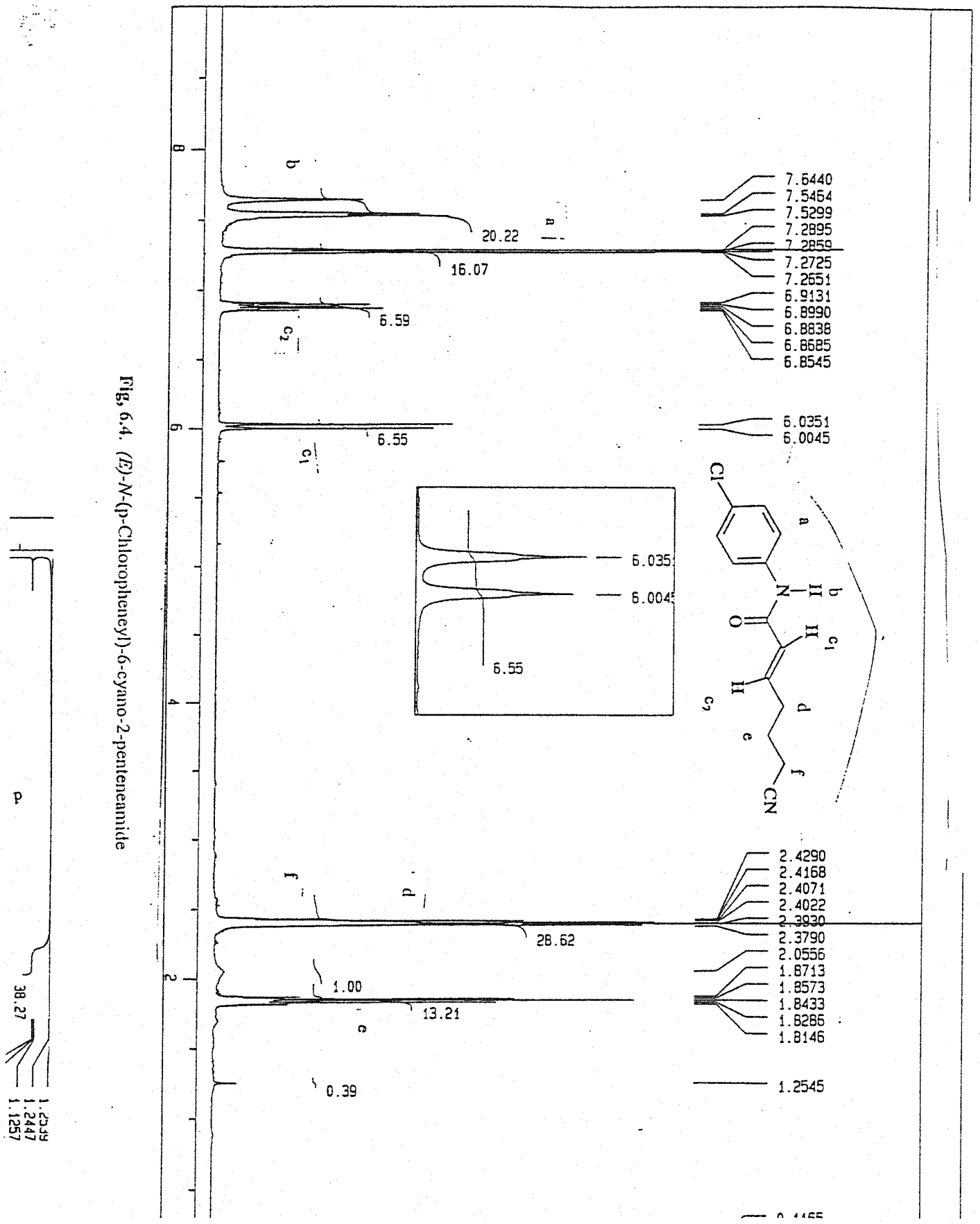



Fig. 6.4. *(E)*-*N*-(p-Chlorophenyl)-6-cyano-2-pentenamide

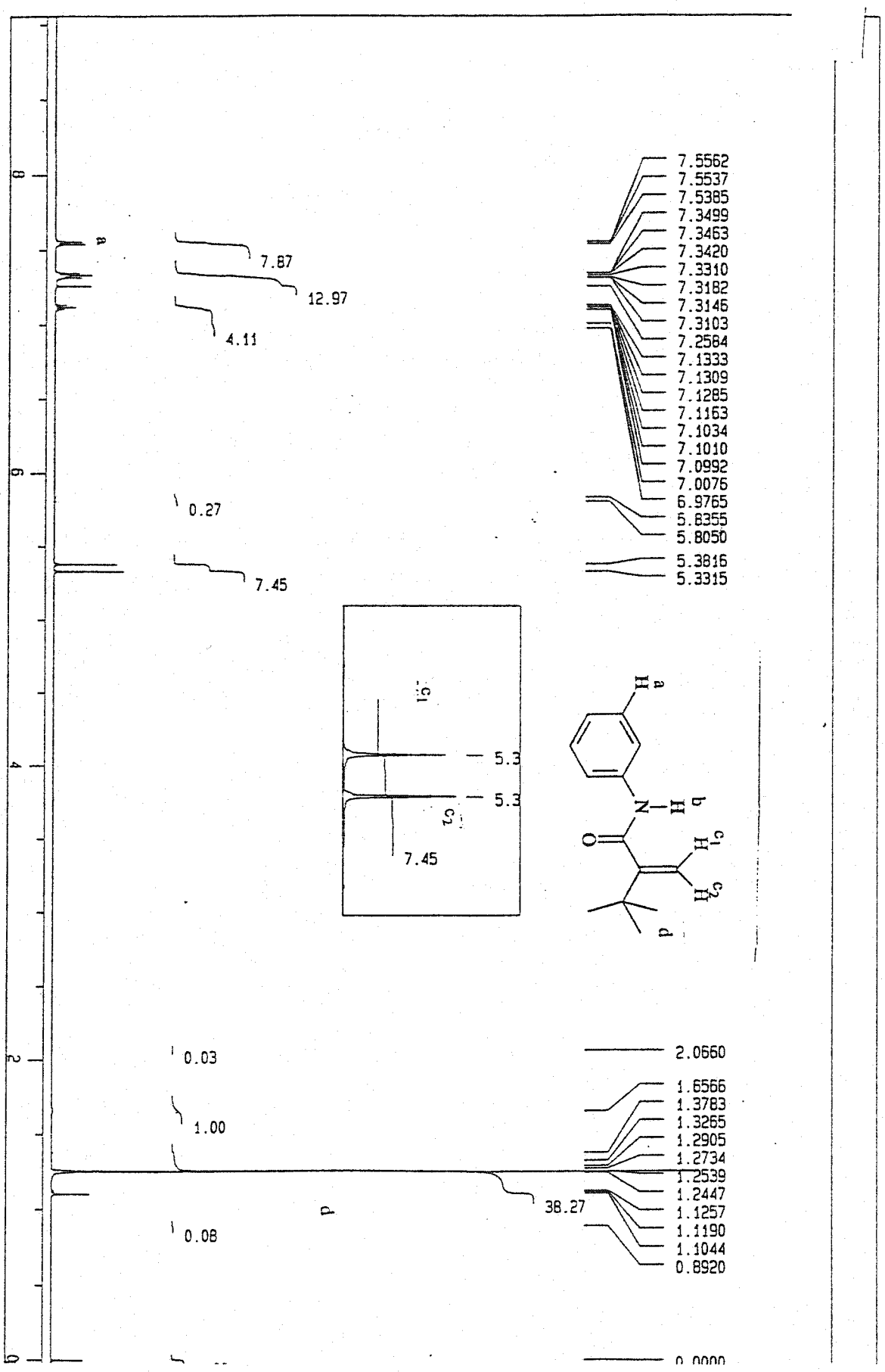



Fig. 6.5. $^1$H NMR of *N*-2-(2,2-dimethylethyl)propeneamide ($\beta$-4.5)

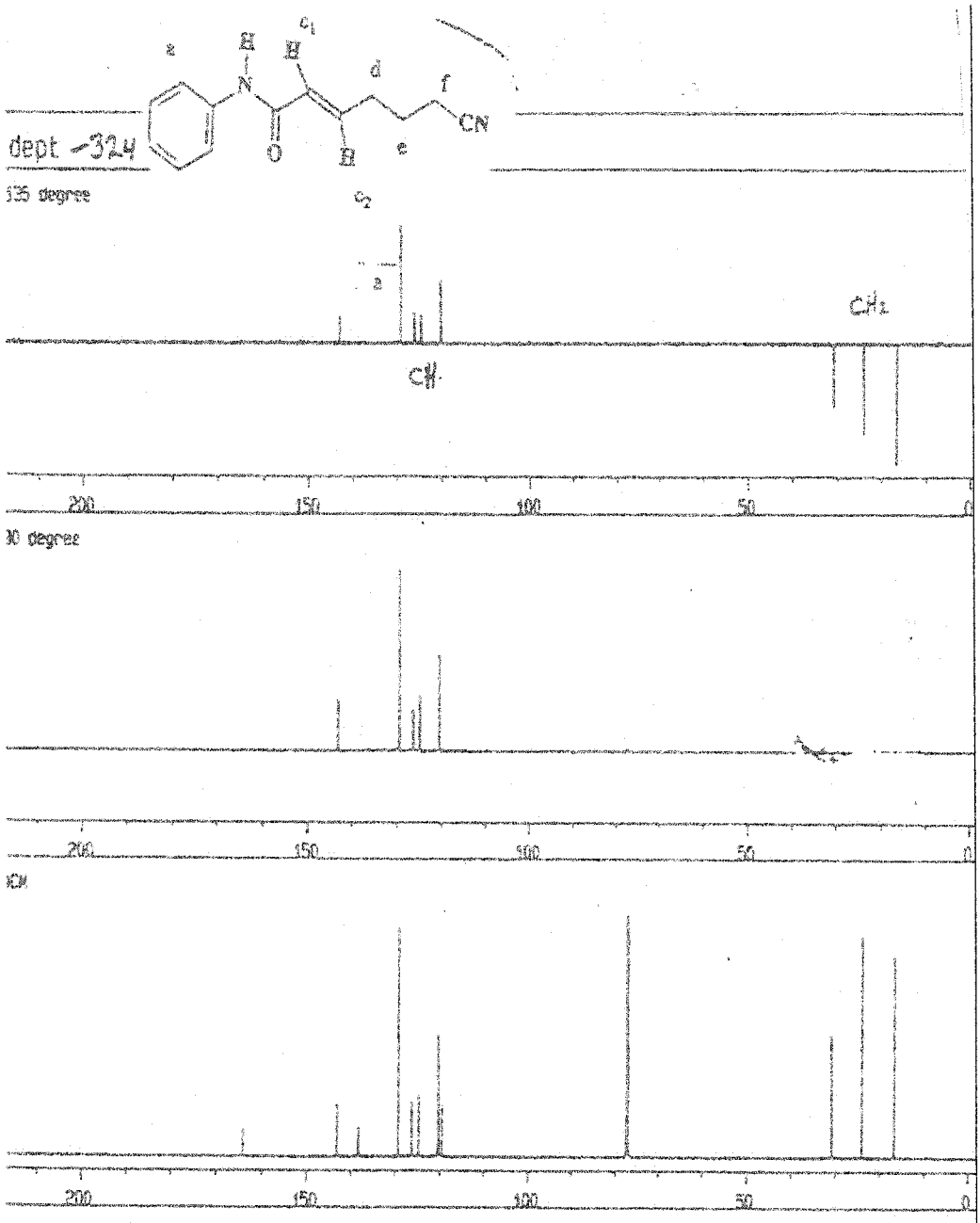



Figure 6.6 Dept $^{13}C$ (δ-9.3)(E)-N-Phenyl-6-cyano-2-pentenamide

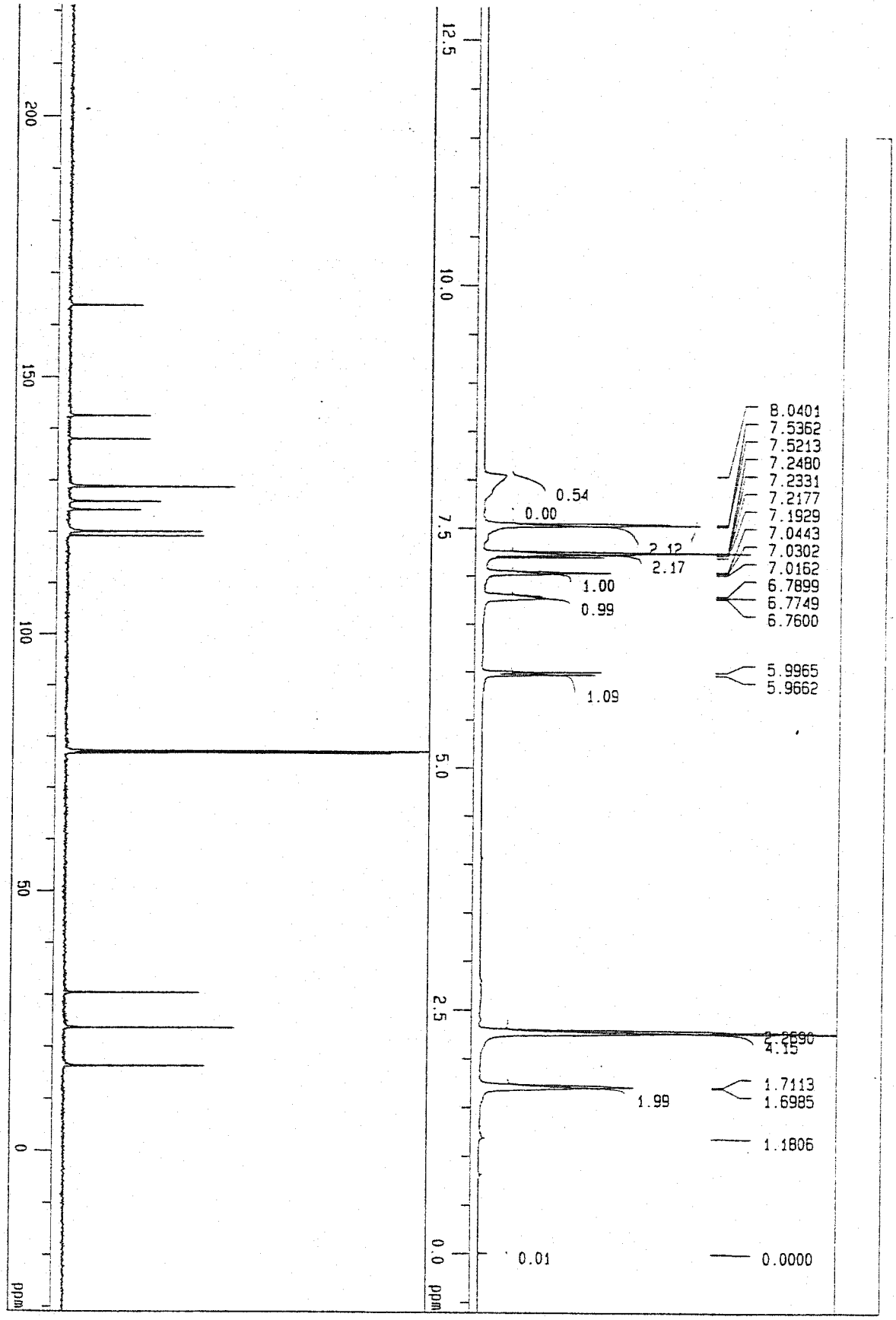



Fig. 6.7. *(E)*-*N*-Phenyl-6-cyano-2-penteneamide

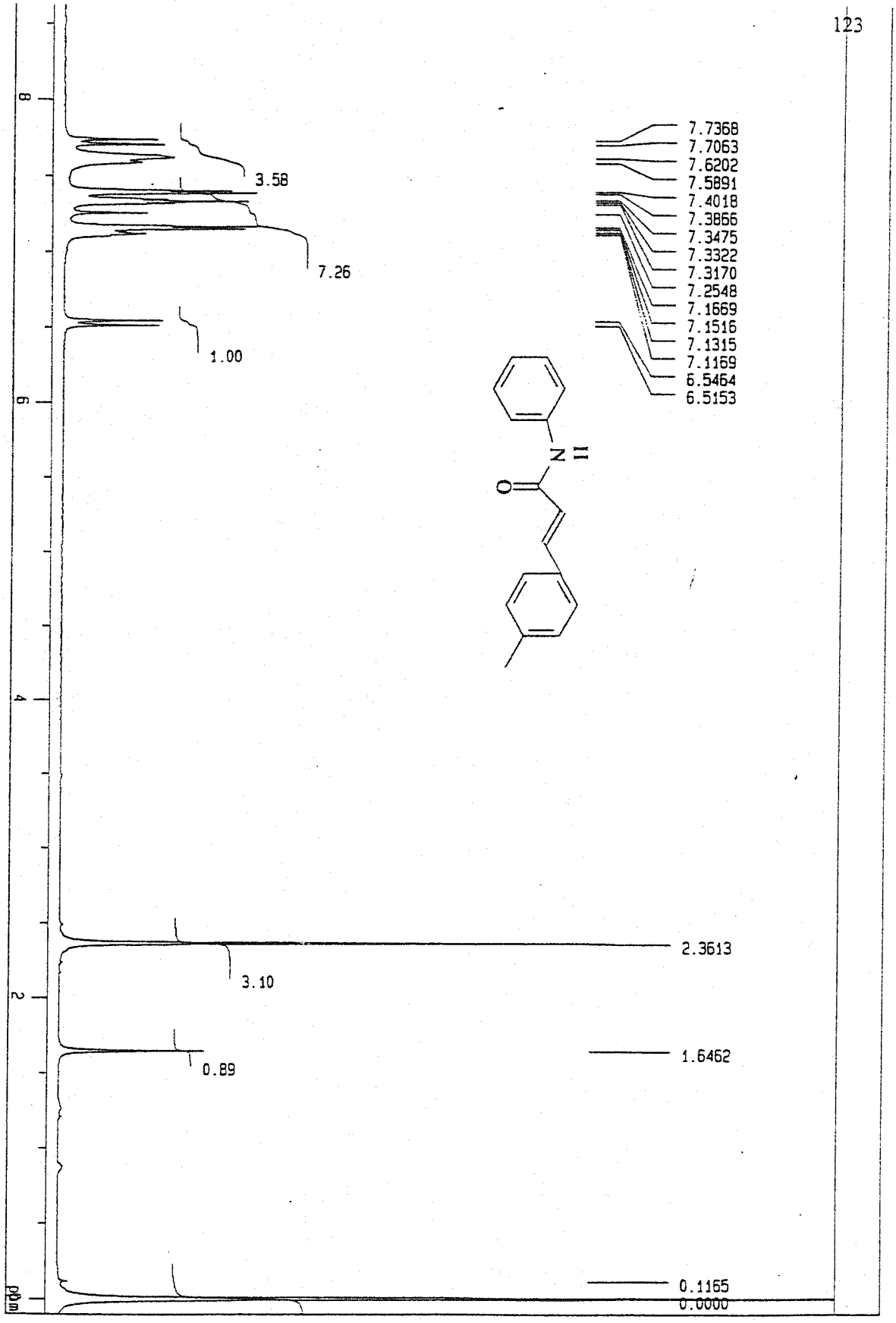
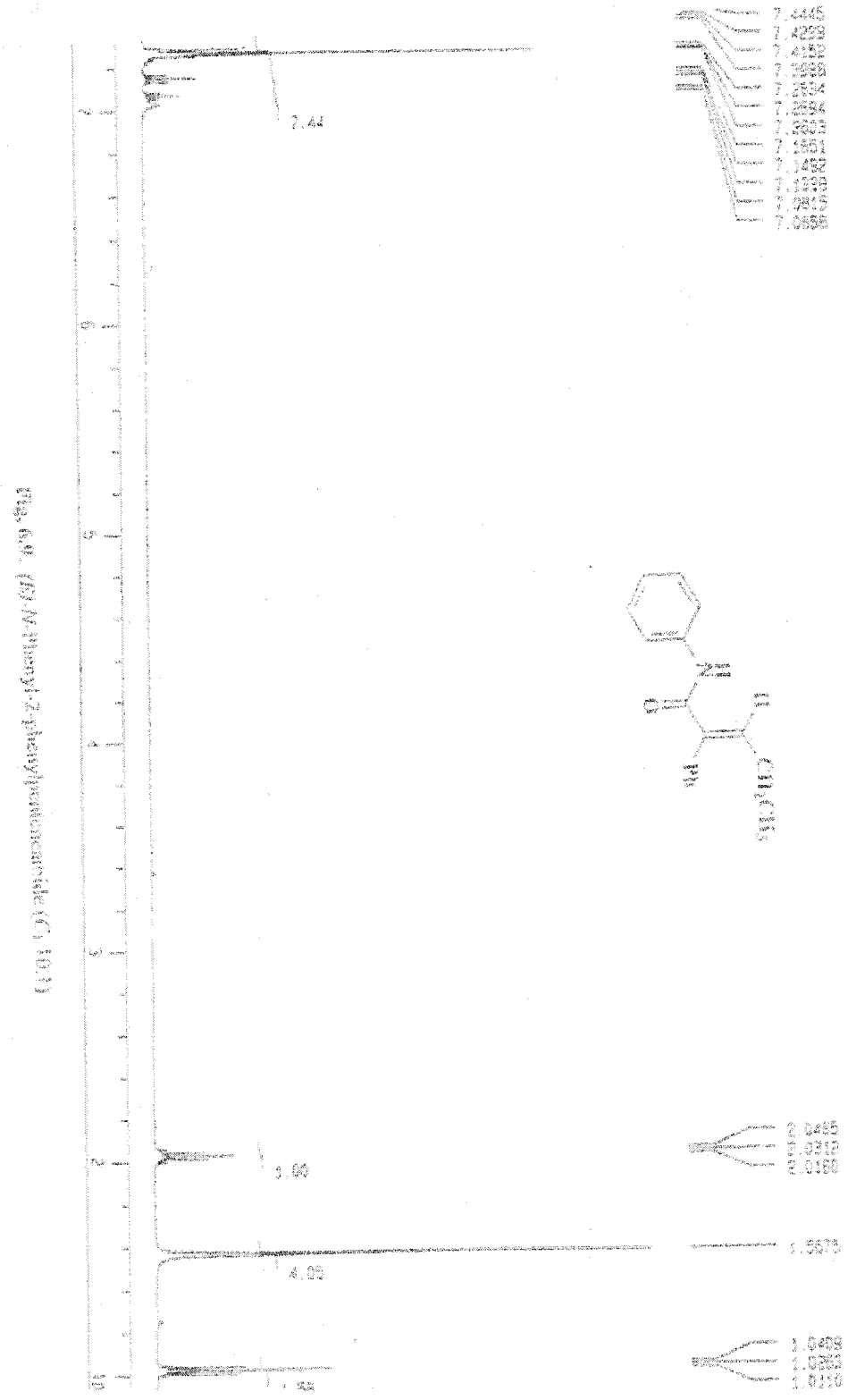



Fig. 6.8. *(E)*-*N*-Phenyl-3-*p*-methylphenylpropeneamide



**Abbreviations**

**Ar** aromatic

**atm** atmosphere

**binap** 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

**br** broad

**Cat** catalyst

**COD** 1,5-cyclooctadiene

**d** doublet

**dba** dibenzylidene acetone

**DIOP** 2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane

**DME** **dimethyl ether**

**dppb** 1,4-bis(diphenylphosphino)butane

**dppe** 1,2-bis(diphenylphosphino)ethane

**dppp** 1,3-bis(diphenylphosphino)propane

**dpppt** 1,5- bis(diphenylphosphino)pentane

**dppm** bis(diphenylphosphino)methane

**Et** ethyl

**eq** equation

**FT** fourier transform

**Hz** hertz, cycle per seconds

**IR** infrared

**J** coupling constant, in Hz

**L** ligand

**m** multiplet

**Me** methyl

**med** medium

**NMR** nuclear magnetic resonance

**$OAc^-$** acetate ion

**$P_{co}$** carbon monoxide pressure

**Ph** phenyl

**$P_{H2}$** hydrogen pressure

**$PPh_3$** triphenylphosphine

**ppm** part per million

**psi** pressure per square inch

**q** quartet

**r.t** room temperature

**s** singlet

**sh** sharp

**t** triplet

**THF** tetrahydorfuran

**TPPTS** triphenylphosphine trisulfonate

**TMS** tetramethylsilane

***p*-TsOH** *p*-toluene sulphonic acid

**ν** wave number

**δ** chemical shift

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   Tetrahedron Lett. 2001, **42**, 12, 2385.
2. B El Ali, **J. Tijani**, A. El-Ghanam, M. Fettouhi,
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